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CRS Annual Meeting Abstract Submission

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Yvonne Perrie Editor



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> FROM THE EDITOR

Editors

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

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

Telephone: +1.651.454.7250 Facsimile: +1.651.454.0766

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

Contact Brianna Plank; telephone +1.651.994.3819, or e-mail at bplank@ scisoc.org for information about exhibiting, advertising, or other visibility opportunities.

Yvonne Perrie University of Strathclyde Glasgow, Scotland



My Last "From the Editor"

Dear Reader.

Welcome again to the CRS Newsletter, which is packed with news and updates on science and our society; we have an update from the New Zealand Chapter and on the 2017 CRS Annual Meeting in Boston-this looks to be a very exciting meeting. We also have an interesting interview with Terry Allen and two nice Scientifically Speaking articles.

This is my last editorial for the CRS Newsletter, as after 12 years as an editor of the newsletter, I am stepping down from the role. It is quite amazing to think how quickly time has passed since I first started work on the CRS Newsletter. The first issue I was involved in as an editor was back in 2004 (www.controlledreleasesociety.org/ publications/Newsletter/Documents/v21i3.pdf). It is great to see that the editors have all aged so well over the last 12 years: we don't look to have changed at all from our photos. Also, many of the standing features that we already had then have stood the tests of time and remain in the newsletter today. A few other ideas (all mine) did not survive so well. In particular, my "Secret Scientist" idea that lasted one issue in 2007 (www.controlledreleasesociety.org/publications/Newsletter/Documents/v24i2. pdf). There was also my editorial on "Colonic Irrigation or Irritation: It Is All in the Title" (www.controlledreleasesociety.org/publications/Newsletter/Documents/v25i2. pdf). This was my investigation into the use of a colon in the titles of papers and abstracts. It was precipitated by a reviewer asking me to remove a colon I had used in a CRS abstract. As I looked back over it today, it reads well, until I spotted the typo in the last sentence. A tad unfortunate, but not to worry. As Thomas Edison said, "I have not failed. I've just found 10,000 ways that won't work."

So it just leaves me to say, enjoy the newsletter-and don't forget to start working on your abstracts for the Boston meeting, so we can all meet up again for some exciting science.

Best regards, Yvonne Perrie

2017 CRS Annual Meeting: Call for Abstracts

Come join us at the 2017 CRS Annual Meeting, where science means business.

Don't miss out on the opportunity to join the best and brightest in delivery science at the CRS Annual Meeting in Boston, July 16–19, 2017. Submit your abstracts now before submissions close January 20, 2017!

Attend the annual meeting to hear prominent scientists discuss the future of delivery science, learn about emerging technologies to solve our industry's challenges, and participate in discussions relevant to the delivery science and technology area.

Abstracts will be accepted in the following session categories:



Advances in Manufacture, Characterization, Stability, and Regulation

This session will cover technology development through scale-up of commercially viable processes and methods to prepare and characterize products designed for controlled release of active materials. Some examples of process technologies include spray drying, hot-melt extrusion, co-precipitation, supercritical fluid technology, fluid bed coating, complex coacervation, 3D printing, inkjet printing, electrospinning, microfluidics, powder layering techniques, high-shear granulation techniques, membrane processes, and emulsion-based processes. The use of quality-by-design (QbD) and safety-by-design (SbD) concepts, analytical technologies for process end-point and real-time monitoring of preparation processes, imaging methods, and other approaches to ensure commercial viability are also critical to this area.

Invited Speakers:

- Diane Burgess, University of Connecticut, U.S.A
- Yue (Helen) Teng, U.S. Food & Drug Administration, U.S.A.

Biologically Active Excipients and Carriers

Most excipients are biologically inert, but there are those such as nonionic surfactants that can enhance absorption of drugs, or that like nonoxynol have a spermicidal effect. Examples of "active" excipients include the cyclodextrin sugammadex injected to bind and thus cease the action of vecuronium. Carrier systems themselves can have the ability to reduce toxin levels. This session hopes to explore and elucidate a wide range of such effects.

Invited Speakers:

- Daniel Kohane, Boston Children's Hospital, U.S.A.
- · Jean-Christophe Leroux, ETH Zurich, Switzerland

Cell Therapies

In silico science and technology have emerged in recent years, contributing to new drug design and development. They offer rational design of drugs. This session will cover all aspects of computational modeling in the field of drug delivery systems across this diverse range of products, including not only formulation and delivery efficiencies but also the microenvironment of tumors and the simulation of blood flow, digitalization of therapies, and so on.

Invited Speakers:

- · Garry Duffy, Royal College of Surgeons in Ireland, Ireland
- David Mooney, Harvard University, U.S.A.

Delivery of Complex and Labile Molecules

The complexity of many new, often macromolecular, therapeutic agents clearly poses problems for their delivery by any route. This session is intended to explore potential avenues for the incorporation of such molecules in appropriate systems to preserve stability and maximize uptake and activity *in vivo*, as well as the challenges that each route of delivery poses. In cosmetic and food applications, labile molecules – often in complex multicomponent mixtures – have to be encapsulated for long-term stability in final formulations and triggered release in the correct ratio. This session also explores solutions for these application areas.

Invited Speakers:

- Victor Balcão, University of Sorocaba, Brazil
- Ana Jaklenec, MIT, U.S.A.

2017 CRS Annual Meeting continued

Delivery of Drug Combinations

In clinical settings, drugs are commonly administered in combination as a means to mitigate their associated toxicities. Recent research in the drug delivery field has sought to identify drug combinations with complementary mechanisms of action and mutually exclusive dose limiting toxicities. This session will focus on the rational identification of efficacious drug combinations as well as their formulation and development.

Invited Speakers:

- Glen Kwon, University of Wisconsin-Madison, U.S.A.
- Yi Yan Yang, Institute of Bioengineering and Nanotechnology, Singapore

Delivery Technologies in Nutraceuticals, Foods, and Oral Products

This session will include all aspects of oral delivery science and product development, including immediate, sustained, delayed, and pulsed release. It includes oral delivery of drugs (from small molecules to biologics), food, feed, beverages, nutrients, nutraceuticals, flavors, probiotics, prebiotics, and supplements. Topics of interest are broad and include, but are not limited to, all aspects of systems that enhance oral absorption, introduce prolonged effect and stability of additives, product acceptability (including taste masking, rheology, etc.), targeted and/or more uniform delivery in the gastrointestinal tract, *in vitro* and *in vivo* models, analytical chemistry, formulation technology for poorly soluble agents, biopharmaceutics, equipment design, and computational modeling.

Invited Speakers:

- Jingyuan Wen, University of Auckland, New Zealand
- Najie Zhang, PepsiCo, U.S.A.

Encapsulation and Controlled Release for Industrial Applications

This session focuses on advances in encapsulation and controlled release products in agrochemicals, agriculture, aquaculture, textiles, coating, adhesive, inks, and other industrial applications. Topics include, but are not limited to, more efficient biomass production for biofuels, genetic engineering (release of genetically engineered materials, enhancing organisms), anticorrosive and/or antifouling coatings (e.g., fish farms or offshore installations), self-healing coatings and materials (e.g., textiles), water storage systems, technologies for high-rise systems (fertilizing, light control), and more traditional areas involving controlled release of nutrients, vaccines, fertilizers, and pesticides.

- **Invited Speakers:**
- To be named

Improving In Vitro Methodologies, Predicting Outcomes

A major obstacle in the development of effective and safe delivery systems is the lack of predictive *in vitro* systems to assess efficacy, tolerability, and immunogenicity. Such predictive assays would enable more efficient *in vitro* screening for down-selection of suitable candidates that are then tested *in vivo*. Within the last years, some progress on the development of more predictive assays has been seen. This session will focus on the recent advances of new methods that address the generation of relevant *in vitro* data that allow for better prediction of *in vivo* behavior of delivery systems.

Invited Speakers:

- Yvonne Perrie, University of Strathclyde, United Kingdom
- To be named

Medical Devices

Versatile types of medical devices have emerged in recent years, contributing to controlled drug administration, distribution, and metabolism. This session will cover all aspects of medical devices in the field of drug delivery systems across this diverse range of products, including microneedles, catheters, devices for regenerative medicines, gels, sutures, contact lenses, and so on.

Invited Speakers:

- Carlo Ĝiovanni Traverso, MIT, U.S.A.
- To be named

Modeling and Simulation: Interplay of Animal and Human Pharmaceutical Development

There is tremendous similarity in the therapeutic needs impacting pharmaceutical product development in humans and dogs. Furthermore, because of their body size, ease of dosing, and ease of handling, the dog is often used as a preclinical species to support human formulation development. Conversely, given the wealth of information generated in support of human drug discovery and product development, human-derived data are often used as "preclinical" information for the dog. Given the significance of this knowledge exchange, it is important to identify those differences in gastrointestinal physiology and drug metabolism that can bias

2017 CRS Annual Meeting continued

conclusions derived from these interspecies extrapolations. With that in mind, this session will provide state-of-the-art information on known differences in dog and human physiologies, explore the potential use of mechanistic models to facilitate the interspecies translation of oral bioavailability data, and provide some examples of how these *in silico* models can be used to support the development of human oral dosage forms.

Invited Speakers:

- Wen Lin, Norvatis, U.S.A.
- Marilyn Martinez, FDA Center for Veterinary Medicine, U.S.A.

New Directions for Polymers in Drug Delivery

Polymer science has been a driving force in drug delivery and delivery of active compounds in other application areas for more than 50 years. Polymeric materials can be rationally designed to control a number of key parameters including material-active interaction, degradability, and biocompatibility. This session will focus on novel approaches in the application of polymer-based materials science to improving drug delivery and delivery of active compounds in other industrial applications.

Invited Speakers:

- Ashutosh Chilkoti, Duke University, U.S.A.
- Nicholas Peppas, University of Texas at Austin, U.S.A.

Ocular Drug Delivery

Loss of eyesight has tremendous impact on quality of life. Treatment of numerous potentially blinding diseases can be improved with sustained, controlled drug delivery. However, the complex anatomy and physiology of the eye make designing effective drug delivery strategies challenging. This session will focus on recent advances in ocular drug delivery, including new materials for long-acting products that can be used to deliver both small and large molecules, surgical implants, remotely triggered drug release, and improved topical formulations.

- **Invited Speakers:**
- Mikhail Ostrovsky, Russian Academy of Science, Russia
- Eliana Souto, University of Coimbra, Portugal

Overcoming Biological Barriers in Drug Delivery

Overcoming biological barriers is one of the major obstacles to the development of efficacious "next generation" delivery systems. The human body has exquisite mechanisms for maintaining health and homeostasis, which limit targeted, controlled, and sustained drug delivery. Similarly, the unique physiology of diseased states potentially presents additional barriers that must be overcome. This session will highlight advances in the development of drug delivery systems to overcome extracellular barriers (mononuclear phagocyte system, blood-brain barrier, blood-retinal barrier, mucosal barriers, tissue barriers, etc.) and cellular barriers (cell uptake, intracellular trafficking, endolysosomal pathway, etc.).

Invited Speakers:

- · Wouter Hinrichs, University of Groningen, The Netherlands
- Christianna Rijcken, Cristal Therapeutics, The Netherlands

YSC Events & Activities at the Annual Meeting in Boston

For the 2017 annual meeting in Boston the Young Scientist Committee (YSC) has come up with an exciting program for the young scientists. Get your career kick started with our new speed mentoring format, where you can talk to experienced people during breakfast in a relaxed atmosphere! Or you can build your network within the community during the Young Scientist Networking Event in a comfortable setting. Sharpen your leadership skills in



our professional development workshop. Before the annual meeting, we will give you tips on oral and poster presentations on the CRS website, so check out the site. Become a part of the YSC and meet us during the conference when we go out on the town! We will make the conference an event that you will remember. See you in Boston!

Still Room at the Bottom: Nano Particles with Macro Impacts

Vishwas Rai¹ and Bozena B. Michniak-Kohn²

Prof. Theresa Mary Allen, a veteran in the drug-delivery field for over 30 years, is a pioneer in the field of long-circulating liposomes and ligand-targeted nanomedicines for anticancer drugs and gene medicines. She has over 200 peer-reviewed publications and is an inventor on several patents. The product Doxil[®] (Caelyx[®] in Europe), the first anticancer nanomedicine approved in the world, came out of pioneering research in her laboratory at the University of Alberta. She has also been active in the area of new drugs from natural products, which has resulted in two drugs proceeding into phase II clinical trials. Her recent work in developing ligand-targeted therapeutics for small molecule therapeutics and gene medicines is at the leading edge of this exciting new field, and the methods she developed are widely used throughout the field. She has given over 270 invited lectures and presentations in over 25 countries around the globe.

She is a founding member and strategic advisor of the Centre for Drug Research and Development (CDRD), which is a novel hybrid organization devoted to advancing promising medical discoveries from academia to a commercially attractive stage. CDRD (www.cdrd.ca) evolved from the recognition by the founders of the pressing need to improve the translation of medical discoveries made in the universities and teaching hospitals into new drugs and technologies that result in economic and health benefits for Canada and beyond. For her scientific work, Dr. Allen has been recognized as a Fellow of the Royal Society of Canada, appeared in *Who's Who in Canada*, and received awards including the International Bangham Award for excellence in liposome research, Cygnus Award (Controlled Release Society) for excellence in guiding graduate student research, Novartis



Terry in her office with a backdrop of research books.

(Controlled Release Society) for excellence in guiding graduate student research, Novartis Award 2000 (Pharmacological Society of Canada), ASTECH Award, and Canadian Society for Pharmaceutical Sciences (CSPS)



Induction into the Royal Society of Canada.

Leadership Award, among many other accolades. She was elected to the CRS College of Fellows in 2012.

She is a registered technologist in medical technology from Ottawa General Hospital (1961) and secured B.Sc. Honours in biochemistry from the University of Ottawa (1965) and a Ph.D. in oceanography from Dalhousie University (1971). She built a strong foundation by performing postdoctoral research training in chemistry, pharmacology, and biochemistry at McGill University, University of Alabama, and University of Miami, respectively. After finishing postdoctoral trainings, she joined the University of Alberta as an assistant professor in pharmacology (1977), where she pursued her research interests for 32 years, rising to the rank of professor. During this time, she also advised a multitude of companies and academic institutions via her consulting service. She currently serves as an adjunct professor at the University of British Columbia in Vancouver, Canada, and is an emerita professor of the University of Alberta. She has an H-index of 81 with 27,720 citations.

Q Please tell us about how your research in the field of oceanography and different postdoctoral trainings ultimately contributed to the successful development of cancer medicine using nanotechnology.

A My interest in medicine began with the training I had in medical technology early in my career and my subsequent undergraduate degree in biochemistry. A longtime interest in the oceans and in scuba diving then led to my acceptance into a Ph.D. program in

¹Independent consultant, 39380 Civic Center Dr., Apt. 416, Fremont, CA, U.S.A. ²Ernest Mario School of Pharmacy, Rutgers–The State University of New Jersey, U.S.A. continued

Allen Interview continued

oceanography at Dalhousie University, with a major in biological oceanography, where I did research at the Fisheries Research Board of Canada in Halifax toward my Ph.D. degree, looking at variations in proteins between different populations of herring. This led to a postdoctoral fellowship at McGill University working on structure and function of the acetylcholine esterase protein, which in turn led to an invitation to join a group at the University of Miami who were doing the first work on the structure and function of the acetylcholine receptor molecule (AchR). The protein was isolated from the electrical organs of the electric ray, and my scuba diving experience was useful in collecting these fish from the Caribbean waters. The AchR was the first receptor to be purified, imaged, and reconstituted into artificial membranes, and my participation in this research led to an interest in liposomes as model membranes. Work with the reconstitution of AchR and band 3 proteins from red blood cells led to a position as a junior faculty member at the University of Alberta.



With Demtri Papahadjopoulos, Alex Bangham, and Dan Lasic in Berlin (all three now deceased).

I continued my contacts with my oceanography colleagues, which led to an invitation to visit Enewetak Atoll (site of the explosion of the first hydrogen bomb) in the Marshall Islands, and I got funding to collect marine invertebrates to screen for new drug activity. Our collections from around the world were screened for cytotoxic activity, and several drugs with potent anticancer activity were identified. Simultaneously, my laboratory was continuing to explore liposomes as model membranes for mechanisms of fusion, reconstitution of membrane proteins, and eventually as drug carriers. This led ultimately to the research from my laboratory that most people at CRS are familiar with in the use of nanoparticles as carriers of anticancer drugs and gene medicines.

Q Please share your experiences with R&D and commercialization of Doxil®, the first anticancer nanomedicine approved in the world.

A Doxorubicin was discovered in the 1950s from the screening of soil-based microbes for anticancer compounds, so it is derived from a natural product. It is still used to treat a wide range of cancers, usually in combination chemotherapy. The severe adverse side effects of this drug, particularly its cardiotoxicity, were known by the late 1960s, so a search began for new formulations of doxorubicin. As early as the mid-1970s, Gregory Gregoriadis and his colleagues were writing about the potential of liposomes as drug carriers, and this coincided with the early clinical use of doxorubicin and recognition of its side effects. Doxorubicin was, therefore, an obvious drug to test in liposomal formulations, and indeed my laboratory and several others began making and testing liposomal doxorubicin formulations in the 1970s. Several problems with the formulations had to be overcome, including increasing its encapsulation, slowing the release rate, and increasing the circulation half-life. In particular, my laboratory became interested in overcoming the rapid removal of liposomes into the mononuclear phagocyte systems, and I went back to my earlier research with red blood cell membranes and screened red blood cell surface molecules for their ability to keep liposomes in circulation. This led to the identification of GM1 as a candidate molecule and my approach to Liposome Technology Inc. (LTI), a new company forming in the San Francisco area, where I had colleagues. The GM1 molecule, although effective, was not ideal. Collaborative research between my laboratory and LTI resulted in the identification of a lipid-anchored PEG molecule for incorporation into the product to be taken to clinical trials. The AIDS epidemic was beginning in San Francisco around that time, and Kaposi's sarcoma was a big problem in those days, so the company identified Kaposi's sarcoma (eligible for fast track approval) for the first clinical trials, leading quickly to the first clinical approval for Doxil[®]. Other clinical approvals followed, including ovarian cancer, multiple myeloma, and breast cancer (except in the United States).

Q How do you look at cancer research in the present compared with five decades ago? In your perspective, has the research community been successful in addressing the disease? What can be done better both scientifically and financially?

A Five decades ago there were few anticancer drugs approved and a lot of possibilities for "low hanging" fruit, so the pace of discovery of new anticancer drugs was rapid. In the intervening decades, most of the "easy" drugs coming from synthetic and natural product research programs were discovered, and many successful combination chemotherapy regimens have been identified. Also, most of the approved drugs that benefited from incorporation into drug delivery systems have been identified and tested, but usually in monotherapy, not in combination. We are just now seeing the successful testing of combination drug products in nanoparticles.

Allen Interview continued

We are in a completely new ball game now, with improved understanding of the molecular mechanisms underlying cancers, the identification of new targets, and the development of personalized medicine approaches to cancer and the use of biomarkers to identify patients that will benefit from newer therapeutics, including gene medicines against new targets. We have also seen huge increases in the complexity and expense of developing new therapeutics against the new molecular targets. The scientific and financial challenges for the development of new oncology therapeutics have increased dramatically, and even more so has the challenge increased to develop successful drug delivery systems for cancer drugs with complexities such as biomarkers, targeting, drug combinations, and so on.

Q Could you please mention some of the current technologies and companies performing research and development in the field of oncology that have potential benefits in the future?

A Some of the more exciting clinical results recently in the drug delivery field have come from three areas: antibody-drug conjugates with several recent approvals (Seattle Genetics, Genentech); delivery of nucleic acids in solid-core lipid nanoparticles, likely to soon receive approval (Alnylam); and delivery of combination small molecule therapeutics in lipid nanoparticles (Celator), with excellent clinical results at the phase III level.

Q Please highlight a few key journal articles published from your research work.

A My most cited articles, all with over 1,000 citations, are those related to the development of long-circulating liposomes and ligand-targeted nanoparticles.

Allen, TM, Cullis, PR. Drug delivery systems: Entering the mainstream. Science 303(5665): 1818-1822 (2004), 2,958 citations. This article outlines the promise of drug delivery systems and has been, of great surprise to me, our most popular article.

Papahadjopoulos, D, Allen, TM, Gabizon, A, Mayhew, E, Matthay, K. Sterically stabilized liposomes: Improvements in pharmacokinetics and antitumor therapeutic efficacy. Proc. Nat. Acad. Sci. 88(24): 11460-11464 (1991), 1,577 citations. Demitri Papahadjopoulos and I were joint first authors on this popular article that was one of the first to talk about the pharmacokinetics and pharmacodynamics of long-circulating liposomes.

Allen, TM, Hansen, C, Martin, F, Redemann, C, Yau-Young, A. Liposomes containing synthetic lipid derivatives of poly (ethylene glycol) show prolonged circulation half-lives *in vivo*. Biochim. Biophys. Acta, Biomembr. 1066(1): 29-36 (1991), 1,292 citations. This was our first popular article showing the use of PEG to make long-circulating liposomes.

Allen, TM. Ligand-targeted therapeutics in anticancer therapy. Nat. Rev. Cancer 2(10): 750-763 (2002), 1,183 citations. Another popular review article that summarized our experience in the development of ligand-targeted liposomal anticancer drugs that showed improved therapeutic outcomes over nontargeted liposomal drugs.



Outreach, South Africa, Council for Scientific and Industrial Research.

Terry with Hannah and Chezy Barenholz in Israel on Chezy's 70th birthday.

Allen Interview continued

- Q Based on your consulting experience, what are some of the major challenges in the field of large-scale manufacturing/R&D of chemicals and biologicals?
- A The new environment of molecular medicine, new pharmacological targets, and personalized therapies presents a considerable challenge for drug delivery systems. Until recently our success came from the use of clinically approved small molecule therapeutics that were usually off patent (so cheaper) and were developed and used as monotherapies with a "one size fits all" approach. Improvements in therapeutic index resulting from these products were often biased toward the reduction in side effects rather than to improvements in response rates. As new targets are being discovered from genetic testing, new therapeutics and more personalized medicine approaches are being adapted to take advantage of these new targets. The result will be that the patient populations who will benefit from these new therapeutics are becoming smaller (even as small as n = 1, in theory), although the response rates to more selectively targeted therapeutics should increase.



Photography hobby on a consulting trip to India.

In the drug delivery area the developmental expenses and the costs of the resulting products are likely to increase substantially. Newer products will contain some or all of the following: combinations of therapeutics, one or more molecules for site-specific targeting, biomarker and/or imaging capabilities, and sensing molecules that can respond to external or internal triggers to control the rate of drug release. As the complexities of the formulations increase, so do the expenses and difficulties associated with their manufacture and quality control. Hence, the development costs will increase and will remain higher than those seen traditionally for small molecule therapeutics or "classical" liposomes. In addition, stakeholder groups are now demanding price/benefit analyses, meaning that new products must demonstrate considerable outcome benefits before they are able to command prices that can recoup the investment in their development.

The research community in the drug delivery field must recognize these new challenges and adapt by developing new approaches more closely aligned with the new reality, since both the scientific and the financial challenges in the current environment have increased exponentially.

Q What are some of your favorite hobbies and travel destinations?

A As many of my colleagues know, I have always enjoyed photography and travel to remote areas with wildlife and interesting cultures—a hobby I share with several of my scientific colleagues (and I have even photographed a few scientific meetings). Since my retirement I continue to consult and advise in the drug delivery area, but I have more time for photography and have developed a website (www.allenfotowild.com) and have started to sell my photographs. Those of you who have visited my house have also seen my organic vegetable garden and greenhouse and have sampled the produce.

Controlled-Release of Blebbistatin to Treat Arthrofibrosis: Inhibiting a Mechanobiological Pathway to Limit Fibrosis

K. Atluri,^a A. M. De Jesus,^b S. Chinnathambi,^b M. J. Brouillette,^c J. A. Martin,^c A. K. Salem,^{a,d} and E. A. Sander^{b,d}

Introduction

Arthrofibrosis is a debilitating and painful condition of the joint that can develop following an injury or surgical procedure.¹ It is characterized by a limited range of motion due to the formation of excessive scar tissue by fibroblasts expressing elevated levels of alpha smooth muscle actin (α -SMA) and enhanced contractile activity compared with normal fibroblasts.² The schematic in Figure 1A illustrates the formation of scar tissue after injury to the human knee joint. These details are more explicitly depicted in the images of a normal and arthrofibrotic goat knee given in Figure 1B. The arthrofibrotic joint contains thick collagen fibers and fibrotic tissue over the cartilage surface.

Current treatments for arthrofibrosis may involve bracing, physical therapy, or surgery, depending on the severity of the condition.³ None of these treatments offer permanent relief, and physiotherapy is often associated with intense pain and swollen joints, even after multiple sessions. Thus, alternative strategies for preventing scar tissue formation are much needed.

Our approach is to target the force generating and sensing machinery of the fibroblast cytoskeleton by employing blebbistatin, a small cell-membrane-permeable molecule that temporarily and reversibly interrupts actin-myosin engagement in a dose-dependent manner.³ This inhibition further results in actomyosin destabilization, perturbed actin organization, and inhibited cellular force generation, all of which should inhibit signaling pathways that promote collagen production. In this study, we evaluated the efficacy of blebbistatin-loaded poly-(lactide-*co*-glycolide) (PLGA) particles to reduce collagen synthesis as a strategy to inhibit fibrosis.

Experimental Methods

Blebbistatin-loaded PLGA particles were fabricated with an oil-in-water single

emulsion technique. Particle size and surface morphology were characterized using scanning electron microscopy (SEM). The release of blebbistatin from PLGA particles was quantified over the course of a week using high-performance liquid chromatography. A collagen gel compaction assay was used to assess the functional effect of blebbistatin-loaded PLGA particles on rabbit joint capsule fibroblast (RJCF) force generation. Collagen production by RJCFs embedded in fibrin gels treated daily with blebbistatin-loaded particles and supplemented with transforming growth factor (TGF) $\beta 1$ and ascorbic acid was quantified by measuring the amount of hydroxyproline in the gels at the end of 10 days.

Results and Discussion

Spherical blebbistatin-loaded PLGA particles were fabricated successfully, with diameters ranging between 0.2 and 6 μ m (Fig. 2A). These particles exhibited a rapid burst release of 68.1% ± 14.8% of the drug over the first 8 h (Fig. 2B) that we attributed to those particles below 1 μ m in diameter. These particles comprised 65% of the total particle population.

continued



Figure 1. (A) Schematic of a human knee joint showing the development of fibrotic scar tissue and an arthrofibrotic joint post injury or surgery. (B) Representative images of normal healthy goat knee (bottom left) and arthrofibrotic goat knee (bottom right). Images courtesy of David Heckelsmiller.

^a Division of Pharmaceutics and Translational Therapeutics, University of Iowa College of Pharmacy, 115 South Grand Avenue, Iowa City, IA 52242, U.S.A.

^b Department of Biomedical Engineering, University of Iowa College of Engineering, 1402 Seamans Center, Iowa City, IA 52242, U.S.A.

^c Department of Orthopedics and Rehabilitation, University of Iowa Roy J and Lucille A Carver College of Medicine, 25 South Grand Avenue, Iowa City, A 52242, U.S.A.

^d Corresponding authors. E-mails: aliasger-salem@uiowa.edu; edward-sander@uiowa.edu

Scientifically Speaking Atluri continued

Significant compaction of RJCF seeded collagen gels was observed with the blank particle treated gels compared with the blebbistatin particle treated gels after 24 h of release from polydimethylsiloxane (PDMS) molds (Fig. 3A). This reduction in gel shrinkage indicated that the blebbistatin particle treatment inhibited cell contractile force generation. The absence of the drug in the blank particle treatment allowed the cells to generate traction forces that significantly reduced gel volume. In addition to quantitative data showing that the drug limited gel restructuring at the microscopic level (data not shown, see reference 4 for details), morphological differences in the presence and absence of blebbistatin were apparent (Fig. 3B). The cells treated with blebbistatin-loaded particles were far less branched and more rounded compared with the cells treated with blank particles (Fig. 3B).

Blebbistatin -loaded PLGA particles also significantly (P < 0.01) limited collagen production (8.8 ± 1.0 µg) compared with the gels treated with either blank PLGA particles (19.5 ± 4 µg) or no particles (17.7 ± 1.8 µg). Furthermore, no significant difference in the collagen content was observed between the gels treated with blebbistatin PLGA particles and the negative control gels (7.2 ± 0.9 µg) that served as a baseline measurement for RJCF collagen production in the absence of TGF- β 1 and ascorbic acid (Fig. 4).



Figure 2. (A) Histogram representing the size distribution of blebbistatin-loaded PLGA particles. The inset of the histogram is a representative SEM image of the particles. (B) Percent cumulative release of blebbistatin from PLGA particles over a week. Results are expressed as mean \pm SD for a sample size of 3. © American Chemical Society; reproduced with permission from Atluri et al.⁴



Figure 3. (A) Representative images showing RJCF seeded collagen gels polymerized in annular PDMS molds and cultured with either blank PLGA particles or blebbistatin-loaded PLGA particles. The red circle denotes the initial gel area, and the white circle denotes the gel area 24 h after treatment. Minimal gel shrinkage was observed when blebbistatin-loaded PLGA particles were administered to the gels, indicating that RJCFs were unable to generate traction forces. (B) Microscope images of the gels in A showing cell morphology. The gels were also embedded with microspheres to facilitate quantification of gel restructuring due to RJCF (see reference 4 for details). An RJCF treated with blank PLGA particles possessed a spindle-shaped morphology typical of a fibroblast, exerting traction forces on the collagen fibers in the gel. An RJCF treated with blebbistatin-loaded PLGA particles lost this morphology and became rounded. Over time, the cell returned to a spindle-shaped morphology (data not shown).



Figure 4. Total collagen produced in RJCF seeded fibrin gels after 10 days of daily treatment with no particles and no TGF- β 1 or ascorbic acid in the medium (negative control), no particles, blank PLGA particles, and blebbistatin-loaded PLGA particles analyzed using hydroxyproline assay. © American Chemical Society; reproduced with permission from Atluri et al.⁴

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Conclusion

By inhibiting cell contractile forces using blebbistatin, collagen production can be significantly reduced. We hope to further develop this technology in order to improve quality of life for arthrofibrotic patients. We hypothesize that long-term protection against the recurrence of fibrosis could be achieved by the sustained delivery of blebbistatin via PLGA particles, such that a single intra-articular injection of these particles immediately after surgical resection would suffice. The use of other drugs that target mechanobiological pathways may also prove useful for treating other diseases.

Acknowledgements

Support for this work was provided by the National Science Foundation (National Science Foundation CAREER CMMI 1452728) to E. A. Sander, the Carver Charitable Trust (#14-4384) to E. A. Sander, the Department of Defense (W81XWH-14-0327) to J. A. Martin, E. A. Sander, and A. K. Salem, and the Lyle and Sharon Bighley Professorship to A. K. Salem. A complete version of this work has been published in the journal *ACS Biomaterials Science & Engineering.*⁴

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Questioning the Rate-Limiting Drug Release and Absorption Mechanisms from an Intramuscular Long-Acting Injectable Prodrug Nano-/Microsuspension: The Effect of Local Macrophage Depletion

Nicolas Darville,^{a,b} Marjolein van Heerden,^c Stefaan Rossenu,^a Guy Van den Mooter,^d Sandra De Jonghe,^c and An Vermeulen^a

Introduction

Long-acting injectable (LAI) (pro)drug nano-/microsuspensions—aqueous dispersions of pure (pro)drug nano-/microcrystals—have shown potential as a drug delivery strategy over the past decade and are now recognized as an attractive formulation option for poorly water-soluble drug candidates intended for chronic therapy. Such formulations are effectively being applied in the treatment of schizophrenia and are currently under clinical investigation for various other indications (e.g., for the treatment and prophylaxis of HIV infection).¹ The slow drug absorption, enabling therapeutic plasma concentrations up to several months following a single intramuscular (i.m.) injection only, is conventionally assumed to be mediated by the physicochemical properties of the compound and the dispersed particles, which drive the slow dissolution rate-limited drug absorption and, hence, the "flip-flop" plasma pharmacokinetics.²

Despite the fact that the (pro)drug dissolution and absorption processes are undeniably determined at least in part by the formulation characteristics, they can also be affected by dynamic interactions with the surrounding tissues.^{3–5} This may explain why the pharmacokinetics often remain difficult to accurately describe, predict, and/or extrapolate relying on empirical instead of mechanistically based modeling approaches.

In an effort to further elucidate the *in vivo* drug release mechanisms that contribute to the often complex pharmacokinetics of LAI nano-/microsuspensions, we recently performed a series of exploratory studies in the rat using a commercially available paliperidone palmitate (PP) LAI suspension.^{5,6} It was hypothesized that the intracellular relocation of the LAI dose within macrophages infiltrating the formulation depot (i.e., part of the normal injection site reaction) leads to the creation of a "secondary" LAI depot, from which the prodrug (PP) dissolution and conversion, and/or paliperidone (active drug; PAL) absorption occur at different rates than under inflammation-free conditions. Therefore, a mechanistic study was conducted to investigate the effect of the injection site reaction, specifically the role of the infiltrating macrophages, on the drug pharmacokinetics after i.m. injection of a PP-LAI suspension in rats.⁷

Experimental Methods

An overview of the study design and objectives is shown in Figure 1. Male adult Wistar rats were divided into two groups. All animals received a single i.m. injection of 20 mgEq/kg of a 1 month PP (i.e., prodrug) LAI nano-/microsuspension (PP-LAI) in the hind leg. In one group, sunitinib malate (SNT), a potent receptor tyrosine kinase inhibitor, and vascular endothelial growth factor (VEGF) receptor antagonist were co-administered daily at a dose of 20 mg/kg orally to suppress the macrophage infiltration and depot neovascularization processes that are part of the injection site reaction occurring after i.m. injection of PP-LAI.⁷

Blood samples were obtained at predetermined time points over a period of 21 and 28 days in co-treated and naïve animals, respectively, for quantification of PAL (active moiety) concentrations in plasma by liquid chromatography



Figure 1. Overview of the applied experimental approach.⁷

continued

^a Quantitative Sciences, Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium.

^b Corresponding author. E-mail: ndarvil@its.jnj.com

^c Preclinical Development and Safety, Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium.

^d Drug Delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, University of Leuven, Leuven, Belgium.

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coupled to tandem mass spectrometry. Non-compartmental pharmacokinetic analysis of the individual PAL plasma concentrationtime profiles was performed, and partial exposure (area under the curve) values until the time of occurrence of relevant histological events were determined for both groups. The calculation of systemic disposition parameter values (e.g., clearance) for comparison between the two groups was supported by pharmacokinetic data obtained in the rat after i.v. dosing of PAL.

A number of animals were sacrificed on day 1, 3, 7, 14, 21, and 28 after injection with PP-LAI, and the isolated i.m. administration sites (i.e., containing the residual formulation depots) were examined histopathologically according to procedures previously elaborated on.⁶ Several key parameters characterizing the i.m. inflammatory and wound healing response, including the extent of macrophage infiltration and accompanied phagocytosis of the PP-LAI particles, were evaluated by microscopy and graded on a scale from 0 to 5 to obtain semi-quantitative data for comparison between the two groups. The histopathological observations were utilized to support the interpretation of the differences in pharmacokinetics between the two groups, as well as for the correlation of some of the pharmacokinetic properties with the local formulation disposition. In addition, a semi-mechanistic nonlinear mixed-effects pharmacokinetic model was developed using the NONMEM[®] software to enable covariate analysis for the identification of factors that might affect the PAL pharmacokinetics in the two groups.⁷

Results and Discussion

Although LAI nano-/microsuspensions are generally well tolerated, the i.m. injected solid (sub)micron-sized particles rapidly agglomerate and are recognized as non-self, leading to localized injection site reactions. Microscopically, such a host response manifests itself as an acute injury-induced inflammation, followed by a foreign body-mediated chronic granulomatous inflammatory reaction.⁵ This chronic healing phase is accompanied by the phagocytosis of large amounts of crystalline PP-LAI. It was demonstrated that the PAL biphasic plasma concentration-time profiles seem to follow the same dynamics as the gradual macrophage infiltration, and a correlation between the amount of PP-LAI phagocytosed and the observed PAL systemic concentrations was found.⁶ As expected, the co-administration of SNT resulted in an almost complete suppression of the granulomatous reaction (i.e., the macrophage recruitment and infiltration) triggered by the i.m. injection of PP-LAI, besides effectively preventing the neovascularization of

the depot (Fig. 2). Representative micrographs showing the extent of the injection site reaction, the infiltration of macrophages, and the neovascularization of the formulation depot after PP-LAI injection, with and without co-administration of SNT, are shown in Figure 2.⁷

The suppression of the injection site reaction by SNT led to delayed and lowered maximum plasma concentrations and resulted in an approximately fivefold reduction of the PAL systemic input rate (cf. flip-flop pharmacokinetics with lower PAL plasma concentrations) (Fig. 3). Pharmacokinetic drug–drug interactions were rejected as possible sources of the observed differences based on literature and on the estimated values of the disposition parameters (e.g., the systemic clearance, calculated using i.v. data for PAL in the rat).⁷ Hence, the observed differences in exposure and terminal decline rate between SNT-treated and naïve animals were attributable to different drug absorption rates (cf. flip-flop pharmacokinetics).

The correlation of the pharmacokinetic data (data not shown) with the histopathological findings indicated that the macrophage infiltration and phagocytosis of an important fraction of the PP-LAI dose contributed to the observed PAL plasma exposures by promoting the prodrug dissolution and/or conversion to the active. The biphasic drug plasma concentration—time profiles following the i.m. injection of a PP-LAI can be seen as a superposition of two concomitant but virtually distinct drug disposition processes (Fig. 3). The initial physicochemistry and particle size-driven fast prodrug dissolution of individual nano-/microcrystals present in the interstitium was rapidly followed by a second,



Figure 2. (Immuno-)histopathology of the rat i.m. administration site 21 days after a single i.m. administration of 20 mgEq/kg PP-LAI without (A–C) and with (D– F) daily oral doses of 20 mg/kg of sunitinib (SNT). The strong suppression of the injection site reaction (i.e., macrophage infiltration and depot neovascularization) by SNT is captured in the semi-quantitative histology scores (G–I; black = PP-LAI only; green = PP-LAI + SNT). H&E = haematoxylin and eosin stain; CD68 = blood-derived macrophages; CD31 = endothelium; * indicates the PP-LAI depot; and arrows indicate capillaries. Low-magnification overview micrographs of the depots are shown as inserts. Figure modified from Darville et al. (2016) and reproduced with permission from Elsevier.⁷

Scientifically Speaking Darville continued

slower, but dominating absorption phase that is determined by the slower prodrug dissolution and by the prodrug conversion rate in the macrophage-infiltrated portions of the LAI depot (Fig. 4).⁷

Accordingly, the PAL plasma concentration–time profiles could be best described assuming an open first-order disposition model with parallel fast (first-order) and slow (sequential zero-firstorder) absorption.⁷ Although the population pharmacokinetic model was not developed with the aim to be fully mechanismbased, the structural model and estimated disposition variables correlated well with the dynamics of the host response. The dual input structure further supports the proposed drug release and absorption mechanism and may thus carry additional mechanistic information that might be relevant to other LAI formulations.

Conclusions

The correlated pharmacokinetic and histopathological findings indicate that the complex multiphasic pharmacokinetics often seen with LAI nano-/microsuspensions are influenced by the local injection site reaction occurring in response to the i.m. nano-/microparticle agglomerate. The hallmark of the local host response, the macrophage infiltration of the formulation depot with subsequent phagocytosis of an important fraction of the PP-LAI dose, modulates the observed biphasic flip-flop pharmacokinetics by promoting the prodrug dissolution and local conversion to the active compound. These fundamental insights might support the implementation of mechanistically more accurate and generic predictive preclinical tools, hence paving the way to a leaner implementation of this LAI formulation technology in the future.

Acknowledgements

This work was supported by a grant from the Agency for Innovation by Science and Technology in Flanders, Belgium (IWT Vlaanderen). This publication is dedicated to the late Patrick Sterkens († May 5, 2016), Senior Scientific Director Preclinical Project Development and Preclinical Development Leader for Paliperidone Palmitate at Janssen Pharmaceutica, Belgium.

PP-LAI only under the probability of the probabili

Figure 3. Left panels: individual and mean (dotted curves) PAL plasma concentration versus time profiles following a single i.m. administration of PP-LAI only (top) and PP-LAI with SNT co-administration (bottom). Right panels: schematic representation and explanation of the two hypothesized contributing drug release and absorption events leading to the observed biphasic flip-flop kinetics.



Figure 4. Schematic representation of the major drug release mechanisms during the chronic phase of the injection site reaction occurring after i.m. injection of LAI nano-/microsuspensions in rodents.

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Drug Delivery and Translational Research Update

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



Special Issue on Ocular Drug Delivery

The issue contains articles by recognized global experts and researchers in the field of ophthalmic drug delivery, covering a broad spectrum of drug delivery topics including current challenges faced with regard to the ocular barriers presented and establishment of suitable models to drive future technology success. The issue is co-edited by Ilva Rupenthal, senior lecturer and director of the Buchanan Ocular Therapeutics Unit at the University of Auckland, New Zealand, and Michael O'Rourke, president of Scotia Vision Consultants, with a track record of launching several products in the market. The total download for the articles published in the issue has already reached over 3,200. The issue is also been highlighted in several media outlets (https://springerlink.altmetric.com/details/13414566/news). See the table of contents at http://link.springer.com/journal/13346/6/6/page/1. DDTR is an official journal of the CRS, and members get free access to the articles published in the journal as a membership benefit.

As an example of this stellar special issue, I would like to highlight two articles—the first a review article and the second a research article. Incidentally, these two are also the most downloaded articles thus far.

Human Corneal Cell Culture Models for Drug Toxicity Studies

Seppo Rönkkö, Kati-Sisko Vellonen, Kristiina Järvinen, Elisa Toropainen, and Arto Urtti Drug Deliv. Transl. Res. 6: 660-675 (2016)

This review gives an overview to the properties of the corneal cell culture models used in ocular toxicity testing. *In vivo* toxicity and absorption studies of topical ocular drugs are problematic, because these studies involve invasive tissue sampling and toxic effects in animal models. Therefore, different human corneal models ranging from simple monolayer cultures to three-dimensional models have been developed for toxicological prediction with *in vitro* models. Each system has its own set of advantages and disadvantages. Use of non-corneal cells, inadequate characterization of gene-expression profiles, and accumulation of genomic aberrations in human corneal models are typical drawbacks that decrease their reliability and predictive power. In the future, further improvements are needed for verifying comparable expression profiles and cellular properties of human corneal models with their *in vivo* counterparts. A rapidly



expanding stem cell technology combined with tissue engineering may give future opportunities to develop new tools in drug toxicity studies. One approach may be the production of artificial miniature corneas. In addition, there is also a need to use large-scale profiling approaches such as genomics, transcriptomics, proteomics, and metabolomics for understanding of the ocular toxicity.

Rapidly Dissolving Polymeric Microneedles for Minimally Invasive Intraocular Drug Delivery

Raghu Raj Singh Thakur, Ismaiel A. Tekko, Farhan Al-Shammari, Ahlam A. Ali, Helen McCarthy, and Ryan F. Donnelly Drug Deliv. Transl. Res. 6: 800-815 (2016)



In this study, authors have developed dissolving microneedles (MNs) fabricated using polyvinylpyrrolidone polymer to enhance ocular drug delivery of macromolecules. *In vitro* studies showed significant enhancement of macromolecule permeation when MNs were used, across both the corneal and scleral tissues, in comparison to topically applied aqueous solutions. Confocal images showed that the macromolecules formed depots within the tissues, which led to sustained permeation. The material used in the fabrication of the MNs was found to be biocompatible with retinal cells (i.e., ARPE-19). Overall, this study reported the design and fabrication of minimally invasive rapidly dissolving polymeric MN arrays that were able to deliver high-molecular-weight molecules to the eye via the intrastromal or intrascleral route.

continued

DDTR Update continued

2017 DDTR Outstanding Research Paper Award

Consider submitting your best research/clinical paper for the 2017 *DDTR* Outstanding Research Paper Award. For consideration, the paper has to be published during the calendar year 2017. Criteria such as translation nature of research, overall impact, innovation, and significance of the study are considered in the selection process. The award is jointly sponsored by Springer-Nature and CRS. The corresponding author will be recognized at the 2018 CRS Annual Meeting & Exposition. Visit the CRS website for further details (www.controlledreleasesociety.org/about/Awards/Pages/DDTROustandingPaper.aspx).

DDTR to Continue Accepting Manuscripts with Negative Data

As announced in 2014, *DDTR* will continue to consider manuscripts reporting negative data, as long as the research is based on a strong rationale or hypothesis. Negative data from one study could provide a rationale or new approach/paradigm to pursue. Also, it would not waste the precious resources in duplicating the same/similar experiments that did not work. Such manuscripts will undergo the standard, rigorous review process as per the journal policy, but the reviewers will be alerted to the nature of the manuscripts. Authors are strongly encouraged to discuss the possible reasons why experiments failed and what alternative approaches or changes to the hypothesis or experimental design might be made.

NZCRS Publication Ethics and Manuscript Writing Workshop

Zimei Wu, Darren Svirskis, and Dedeepya Uppalapati School of Pharmacy, University of Auckland, New Zealand

In June 2016, the New Zealand Local Chapter of the Controlled Release Society (CRS) hosted David W. Grainger (University of Utah, U.S.A.) for an educational workshop at the Faculty of Medical and Health Sciences, University of Auckland. Prof. Grainger shared his vast expertise in scientific writing as an editorial board member for six major journals and an author of 176 full research papers and 23 book chapters. He challenged the audience on their understanding of good science versus bad science and shared his knowledge on what makes a good research paper.

Through his passion and as a result of high levels of engagement with the interested audience, this 1.5 hour writing workshop was extended to 2 hours, which was immediately followed by his 1 hour research seminar titled "Local Delivery of Bioactive Agents from Surgically Placed Implants."



David Grainger presents on how to write a good research paper.

More than 60 students and academics were in attendance. Afterward, many of the attendees requested and were given copies of the presented slides for themselves and to share with their colleagues who could not attend. Prof. Grainger's visit was finished with small group discussion with Auckland NZCRS members, joined by Peter Hunter, distinguished professor and director of Auckland Bioengineering Institute, and Jillian Cornish, School of Medicine, which promoted the CRS.



Rapt audience at the workshop.



NZCRS president Zimei Wu thanks David Grainger.

People in the News

Compiled by Steven Giannos, University of Texas Medical Branch, Galveston, TX, U.S.A.

CBSET Appoints Rami Tzafriri, Ph.D., as Director of Research and Innovation

Business Wire: October 28, 2016 – LEXINGTON, MA, U.S.A. – CBSET Inc. announced today that it has appointed Dr. Rami Tzafriri as director of research and innovation. Since 2009, Dr. Tzafriri has held the position of principal scientist at CBSET, where he developed quantitative computational and experimental methods for evaluating combination drug and energy delivery devices. He is best known for his publications on the mechanisms underlying the biological effects of drug-eluting stents and renal denervation RF catheters.

In his new role, Dr. Tzafriri will provide scientific direction to CBSET's cutting-edge translational research programs, leveraging institutional strengths in histopathology, interventions, imaging, bioanalysis, and computational modeling. In support of this mission, Dr. Tzafriri has established postdoctoral fellowship and predoctoral internship programs, where promising young scientists are hosted for 1–3 years to work alongside CBSET researchers and key opinion leaders (KOLs). The program aims to accelerate the development of novel *in vivo* and bench models and help CBSET's sponsors translate their ideas into breakthrough therapies. These efforts will allow CBSET to continue to generate high-profile research publications that impact medical innovation.

"CBSET offers a unique opportunity for top innovators to evaluate novel therapies in an environment that combines high-level scientific expertise, speed in innovation, and rigorous regulatory compliance. Our approach to translational research has enabled shortened product development timelines and impactful product differentiation for several novel technology platforms. The appointment of a director of research and innovation aligns with CBSET's corporate vision of growth through investment in scientific collaboration, technology advancement, and novel method development," said Peter M. Markham, president and CEO. "Dr. Tzafriri's wealth of experience in directing complex quantitative research programs in a fast-paced CRO environment combined with his ability to effectively communicate our novel findings to R&D scientists and clinicians throughout the world make him a perfect fit for this role."

"I am excited by this opportunity to direct CBSET's research and education missions and look forward to collaborating with an expanding array of industry, academic partners, and KOLs," said Dr. Tzafriri. "Medical therapies are inherently complex and best understood using an integrative approach that combines quantitative experiments with computational modeling. CBSET is a leader in this area, and the new role and the associated resources will allow us to use this paradigm in an expanded range of therapeutic areas for the benefit of our sponsors and the advancement of innovative therapies."

Dr. Tzafriri holds an M.Sc. in physics and received his Ph.D. from the Hebrew University of Jerusalem for his research on biodegradable controlled-release devices and their use in the treatment of gingivitis and mammary tumors. He later held a postdoctoral research position in Dr. Elazer Edelman's laboratory at MIT, with a focus on the development of *ex vivo* and computational models to examine how blood flow and receptor-ligand interactions affect drug distribution in arteries and in the myocardium.

CBSET Inc., 500 Shire Way, Lexington, Massachusetts, is the preclinical research leader in critically important therapeutic fields such as interventional cardiology, renal disease and dialysis, chronic drug-resistant hypertension, women's health, minimally invasive surgery, orthopedics, biological and synthetic tissue repair, drug delivery, bioresorbable devices, and combination medical device and drug-eluting products. Learn more about CBSET's expert biomedical research services or please contact us. cbset.org

Noven Appoints Ralph Lipp, Ph.D., as Vice President and Chief Scientific Officer

Business Wire: October 3, 2016 – MIAMI, FL and NEW YORK, NY, U.S.A. – Noven Pharmaceuticals, Inc., today announced the appointment of Ralph Lipp, Ph.D., as the company's new vice president and chief scientific officer. In this role, Dr. Lipp will lead all research and development efforts for Noven's transdermal drug delivery programs and related product development activities. Dr. Lipp will report to Jeff Mihm, chief executive officer.

Dr. Lipp has more than 25 years of experience in transdermals and drug delivery including 14 years at Schering AG, where he rose to the position of head of pharmaceutical development. He also served as the vice president pharmaceutical sciences R&D at Eli Lilly, where he was responsible for successfully managing a portfolio of new chemical and biological entities plus life cycle management projects in all phases of clinical development. Dr. Lipp joins Noven from Lipp Life Sciences LLC, a firm he founded in 2012, which

People in the News continued

focused on advising clients in the areas of innovation strategy, innovation process, technology assessment, R&D portfolio review, and marketed products. Dr. Lipp has also been serving as a founding advisory board member for the Catalent Applied Drug Delivery Institute.

Dr. Lipp has more than 130 publications in the area of pharmaceutical science and drug delivery, including over 20 patents covering five marketed medicines. He earned his Ph.D. in medicinal chemistry from Freie Universität Berlin in Berlin, Germany.

"I am pleased to have Dr. Lipp leading Noven's research and development efforts," said Jeff Mihm. "His extensive experience in transdermals and drug delivery, combined with his successful record of leadership, will broaden our development programs and, ultimately, help Noven to deliver meaningfully differentiated products to advance patient care."

Noven Pharmaceuticals, Inc., is a specialty pharmaceutical company engaged in the research, development, manufacturing, marketing, and sale of prescription pharmaceutical products. Noven's mission is to develop and offer pharmaceutical products that meaningfully benefit patients around the world, with a commitment to advancing patient care through transdermal drug delivery. Noven is a standalone operating subsidiary of Japan-based Hisamitsu Pharmaceutical Co., Inc., serving as Hisamitsu's U.S. platform in prescription pharmaceuticals, and helping Hisamitsu bring the benefits of patch therapy to the world. For more information about Noven, visit www.noven.com. For information about Hisamitsu, visit www.hisamitsu.co.jp/english.

Companies in the News

Compiled by Steven Giannos, University of Texas Medical Branch, Galveston, TX, U.S.A.

November

FDA Accepts Genentech's Biologics License Application for Subcutaneous Formulation of Rituximab

PRNewswire: November 3, 2016 – SAN DIEGO, CA, U.S.A. – Halozyme Therapeutics, Inc. (NASDAQ: HALO) today announced that the U.S. Food and Drug Administration (FDA) has accepted Genentech's Biologics License Application for a subcutaneous formulation of rituximab in multiple blood cancer indications. This is a co-formulation with Halozyme's proprietary recombinant human hyaluronidase enzyme (ENHANZE[™] platform), approved and marketed under the MabThera[®] SC brand in countries outside the United States.

"We are excited to see Genentech and Roche taking steps to bring a subcutaneous formulation of rituximab to patients in the United States," said Dr. Helen Torley, president and chief executive officer. "If approved, this formulation has the potential to reduce administration time for patients and health care practitioners."

Halozyme Therapeutics is a biotechnology company focused on developing and commercializing novel oncology therapies that target the tumor microenvironment. Halozyme's lead proprietary program, investigational drug PEGPH20, applies a unique approach to targeting solid tumors, allowing increased access of co-administered cancer drug therapies to the tumor in animal models. PEGPH20 is currently in development for metastatic pancreatic cancer, non-small cell lung cancer, gastric cancer, metastatic breast cancer, and has potential across additional cancers in combination with different types of cancer therapies. In addition to its proprietary product portfolio, Halozyme has established value-driving partnerships with leading pharmaceutical companies including Roche, Baxalta, Pfizer, Janssen, AbbVie, and Lilly for its ENHANZE[™] drug delivery platform. Halozyme is headquartered in San Diego. For more information, visit www.halozyme.com.

Windtree Therapeutics Preclinical Study Results Show Potential for KL4 Surfactant as Possible Medical Countermeasure to Radiation Exposure

PRNewswire: November 3, 2016 – WARRINGTON, PA, U.S.A. – Windtree Therapeutics, Inc. (Nasdaq: WINT), a biotechnology company focused on developing aerosolized KL4 surfactant therapies for respiratory diseases, announced today that recently presented preclinical data at the 62nd Radiation Research Society Annual Meeting suggest that KL4 surfactant could potentially be an effective medical countermeasure to mitigate acute and chronic/late-phase radiation-induced lung injury (pneumonopathy) due to exposure from a nuclear accident or act of terrorism. The company believes that, as a possible additional application, KL4 surfactant may also mitigate radiation pneumonopathy associated with cancer radiation therapy.

"While we remain primarily focused on the rigorous and timely execution of the AEROSURF[®] phase 2 clinical development program for premature infants with respiratory distress syndrome (RDS), a phase I SBIR grant of \$600,000 from the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) provided us the opportunity to explore the use of KL4 surfactant to mitigate damage to lungs after radiation exposure," commented Craig Fraser, president and chief executive officer. "We are very encouraged by the results of this early preclinical work and are grateful for the support provided by the NIH. Based on the results of this initial study, Windtree was awarded \$3 million in additional funding from the NIAID to support the further exploration of aerosolized KL4 surfactant as a potential medical countermeasure for radiation exposure."

In this initial study, KL4 surfactant was administered via an intranasal route into the lungs of C57/BL6 mice 24 hours following exposure to a single fraction of high-dose (13.5 Gy) thoracic-targeted X-ray irradiation (XRT). Mice were evaluated for evidence of reduced blood oxygenation and lung inflammation between two to four weeks post-XRT, and lung fibrosis, chronic pneumonitis, oxidative stress, and local and systemic inflammation at 18 weeks post-XRT, by assessing lung function and analyzing bronchoalveolar fluid (BALF), serum, and lung tissue.

The data from this study indicate that KL4 surfactant treatment significantly preserved blood oxygenation in irradiated mice two and four weeks post-XRT, suggesting reduced acute lung injury, coupled with significantly reduced lung inflammation in irradiated mice three and 18 weeks post-XRT. KL4 surfactant-treated irradiated mice also showed a decrease in lung fibrosis and pneumonitis at 18 weeks post-XRT, evidence of reduced chronic/late-phase radiation-induced lung injury.

"Though an early study, these data are especially encouraging as the U.S. Department of Health and Human Services has indicated that there is an urgent and unmet need to develop medical countermeasures to prevent radiation pneumonopathy that can be efficiently administered within days, if not hours, post-exposure. These data combined with our promising work to deliver aerosolized KL4 surfactant represent progress toward potentially providing an effective and efficient means to counter exposure to potential radiation lung damage under various circumstances, including potentially as a result of cancer radiation therapy," said Robert Segal, M.D., senior vice president, clinical development and academic affairs, Windtree Therapeutics, the study principal investigator, who conducted this research in collaboration with Melpo Christofidou-Solomidou, Ph.D., research professor of medicine at the University of Pennsylvania.

Exposure to ionizing radiation (IR) from an unpredictable nuclear reactor accident, a nuclear attack, or deliberate terrorist actions, including the detonation of a radiological dispersal device (RDD), represents a significant public health concern. Radiological and nuclear threats are complex, as the radiation source, duration, and extent of exposure all contribute to the nature and effects of IR exposure. The lung is particularly susceptible to injury from IR-exposure from external radiation sources, as well as from inhaled radioactive particles from nuclear radioactive fallout as an example. Radiation pneumonopathy can manifest with acute radiation pneumonitis (ARS) and/or delayed effects of acute radiation exposure (DEARE), which may lead to progressive, often fatal, pulmonary fibrosis many months or years later, with a median survival of 2 to 4 years. This is also seen with pulmonary radiation exposure as a result of radiation therapy for certain types of cancer.

This preclinical study of KL4 surfactant as a potential medical countermeasure to mitigate acute and chronic/late-phase radiationinduced lung injury was supported, in part, by a \$0.6 million phase I Small Business Innovation Research (SBIR) grant from the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under award number R43AI102308. The follow-on phase II SBIR \$3.0 M grant supporting ongoing research of aerosolized KL4 surfactant as a radioprotectant is being funded under award number R44AI102308. The content of this press release is solely the responsibility of Windtree Therapeutics, Inc., and does not necessarily represent the official views of the National Institutes of Health or the University of Pennsylvania.

Windtree Therapeutics, Inc. is a clinical-stage biotechnology company focused on developing novel surfactant therapies for respiratory diseases and other potential applications. Windtree's proprietary technology platform includes a synthetic, peptide-containing surfactant (KL4 surfactant) that is structurally similar to endogenous pulmonary surfactant and novel drug-delivery technologies being developed to enable noninvasive administration of aerosolized KL4 surfactant. Windtree is focused initially on improving the management of respiratory distress syndrome (RDS) in premature infants and believes that its proprietary technology may make it possible, over time, to develop a pipeline of KL4 surfactant product candidates to address a variety of respiratory diseases for which there are few or no approved therapies.

Windtree's lead product candidate is AEROSURF[®], a novel, investigational drug/device product that combines the company's proprietary KL4 surfactant and aerosolization technologies. AEROSURF is being developed to potentially reduce or eliminate the need for endotracheal intubation and mechanical ventilation in the treatment of premature infants with respiratory distress syndrome (RDS). Enrollment is ongoing in a phase 2b clinical trial in up to 240 premature infants to study AEROSURF in premature infants 29 to 32 week gestational age receiving nasal continuous positive airway pressure (nCPAP) for RDS, compared with infants receiving nCPAP alone. The phase 2b trial is a global trial with clinical sites in North America, Europe, and Latin America. For more information, please visit the company's website at www.windtreetx.com.

Elixir Medical Corporation Announces Excellent Six-Month Safety and Efficacy Results for Thin-Strut DESolve™ Cx Novolimus Eluting Bioresorbable Coronary Scaffold System

Business Wire: November 1, 2016 – SUNNYVALE, CA, U.S.A. – Elixir Medical Corporation, a developer of products that combine state-of-the-art medical devices with advanced pharmaceuticals, today announced excellent six-month clinical data for the first 25-patient subset of the DESolveTM Cx Clinical Study at the 28th annual Transcatheter Cardiovascular Therapeutics (TCT) Conference in Washington, DC. The DESolve Cx novolimus eluting bioresorbable coronary scaffold has a strut thickness of 120 μ m and degrades within one year, returning the patients' coronary vessel to its normal *de novo* state. The DESolve Cx scaffold is more deliverable and designed to address the needs of a broader patient population.

At 6 months in the 25 patients, Elixir's DESolve Cx demonstrated excellent late lumen loss of 0.18 ± 0.29 mm, no cases of scaffold thrombosis, and no (0%) clinically driven major adverse cardiac events. Imaging results by IVUS (intravascular ultrasound) demonstrated low neointimal volume obstruction of 5%. IVUS also showed an increase in scaffold and lumen volume between baseline and six months, also confirming early uncaging of the vessel. Excellent acute scaffold strut apposition and embedding was observed

with intravascular optimal coherence tomography (OCT) imaging. The patients were enrolled in Europe and Brazil, and will continue to be followed-up through two years. The six-month results of the entire study population will be presented after follow-up completion.

The DESolve Cx clinical trial is a 50-patient, single-arm, multi-center, evaluation of the Elixir's thin-strut DESolve Cx novolimus eluting bioresorbable coronary scaffold system. The primary imaging endpoint of the study is in-stent late lumen loss assessed by quantitative coronary angiography (QCA) at six months. The primary clinical endpoint is MACE (major adverse cardiac events), a composite of cardiac death, target vessel MI (myocardial infarction), and clinically indicated target lesion restenosis at six months. Secondary endpoints include MACE at 30 days and at 12 and 24 months; in-segment late lumen loss, binary restenosis, and percent diameter stenosis by QCA; in-scaffold percent volume obstruction and malapposition with IVUS (intravascular ultrasound); and in-scaffold percent obstruction and strut coverage with OCT (optical coherence tomography).

Profs. Alexandre Abizaid, M.D., Ph.D., of the Instituto Dante Pazzanese de Cardiologia, Brazil, and Stefan Verheye, M.D., Ph.D., ZNA Middleheim Hospital, Antwerp, Belgium, are the co-principal investigators of the DESolve Cx international study.

"The trial results position DESolve Cx as a strong next-generation bioresorbable scaffold system providing physicians with a promising product to improve clinical outcomes in a broad patient population," said Dr. Abizaid. "I'm confident that Elixir's DESolve Cx coronary scaffold system has the potential to become a work-horse product that will be competitive with the best-in-class drug eluting stent systems in the clinic, and has the added advantage of being completely resorbed into the body and return vessels to a *de novo* state."

"I was pleased with the acute outcomes of the procedure with DESolve Cx, and now I'm excited that the results for these initial patients continue to look excellent at 6 months," said Dr. Verheye.

"The 6 month results for the DESolve Cx patients reinforce Elixir's commitment of providing cardiologists with the most deliverable and user-friendly coronary scaffolds in order to realize greater adoption in everyday clinical practice," said Motasim Sirhan, chief executive officer of Elixir Medical. "Elixir is proud to present one of the broadest and most innovative portfolios of coronary scaffolds that will help physicians realize their goal of treating and returning the patient's coronary arteries to their *de novo* state."

The fully bioresorbable DESolveTM Cx scaffold system, developed from a proprietary and proven poly-L-lactide (PLLA)-based polymer, provides optimal strength and support to the artery while delivering the novel anti-proliferative drug novolimus. The unique attributes of the DESolve Cx scaffold system include its ability to (a) demonstrate lumen area increase at six months demonstrating vascular restoration; (b) degrade within one year designed to eliminate late scaffold-related events; (c) maintain radial strength and vessel support for the necessary period of vessel healing while degrading; and (d) have a wide margin of expansion.

Elixir Medical has also announced excellent 4 year clinical and imaging results from the DESolve Nx international pivotal clinical trial for the CE Mark-approved, fully bioresorbable DESolve[®] novolimus eluting coronary scaffold system. Prof. Alexandre Abizaid, M.D., Ph.D., of the Instituto Dante Pazzanese de Cardiologia, Brazil, and co-principal investigator of the DESolve Nx Trial, presented the clinical and imaging results to a packed audience of the international cardiology community gathered at the 28th annual TCT (Transcatheter Cardiovascular Therapeutics) Conference in Washington, DC.

The DESolve[®] scaffold is completely resorbed in the vessel wall within 18 and 36 months, and at the four year end point, well after full resorption, the system continues to show a low overall MACE rate (9.0%) with no definite stent thrombosis.

"The DESolve scaffold has been completely resorbed for some time now, and I'm delighted to see sustained and excellent long-term results and patent vessels in patients" said Dr. Abizaid. "The golden tube formation within 18 to 36 months and the continued low incidence of MACE through 4 years clearly reinforces the unparalleled advantage of DESolve Nx over other modes of treatment, and even expands its potential for evaluation in new clinical indications."

"DESolve remains the only bioresorbable scaffold in the world that achieves lumen gain at 6 months while maintaining excellent safety and patency rate up to 4 years," said Motasim Sirhan, chief executive officer of Elixir Medical.

DESolve Nx pivotal trial enrolled 126 patients at 13 centers in Europe, Brazil, and New Zealand. At 6 months, Elixir's DESolve demonstrated excellent mean late lumen loss of 0.20 ± 0.32 mm as measured by QCA. IVUS imaging results demonstrated a statistically significant increase of 9% in the lumen area between post procedure 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.

The fully bioresorbable DESolve scaffold system, developed from a proprietary and proven poly-L-lactide (PLLA)-based polymer, provides optimal strength and support to the artery while delivering the novel anti-proliferative 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) degrade within one year designed to eliminate late scaffold-related events; (c) its ability to maintain radial strength and vessel support for the necessary period of vessel healing while degrading; and (d) its ability to have a wide margin of expansion.

Elixir Medical Corporation, a privately held company headquartered in Sunnyvale, California, develops products that combine stateof-the-art medical devices with advanced pharmaceuticals to provide innovative treatment solutions to patients worldwide. The company's next-generation drug-eluting stent systems and bioresorbable coronary scaffold are designed to optimize localized drug delivery to provide safe and effective treatments for cardiovascular patients. For more information, visit www.elixirmedical.com.

October

Intec Pharma Granted Chinese Patent for Accordion Pill™ Carbidopa/Levodopa

Business Wire: October 31, 2016 – JERUSALEM, Israel – Intec Pharma Ltd. (NASDAQ: NTEC) (TASE: INTP), a clinical-stage biopharmaceutical company focused on developing drugs based on its proprietary Accordion Pill[™] platform technology, announced that the State Intellectual Property Office of the People's Republic of China (SIPO) has granted a Chinese patent for an Accordion Pill containing certain drugs, including the combination of carbidopa and levodopa. The patent, granted under number ZL 200980120103.9, is titled "Carbidopa/Levodopa Gastroretentive Drug Delivery" and is currently scheduled to remain in force until April 2029. The patent belongs to the company's IN-7 patent family, which already includes patents granted in the United States, Europe, and Israel.

"We continue to globally expand and strengthen our patent portfolio for our IN-7 patent family in order to build a fortress intellectual property position that will protect our Accordion Pill technology platform," stated Zeev Weiss, chief executive officer of Intec Pharma. "This Chinese patent secures key elements of our Accordion Pill technology platform and our leading product, the Accordion Pill Carbidopa/Levodopa, in significant markets. The Accordion Pill Carbidopa/Levodopa is currently in a global phase III clinical trial in advanced Parkinson's disease."

Intec Pharma Ltd. is a clinical stage biopharmaceutical company focused on developing drugs based on its proprietary Accordion Pill[™] platform technology. The company's Accordion Pill is an oral drug delivery system that is designed to improve the efficacy and safety of existing drugs and drugs in development by utilizing an efficient gastric retention and specific release mechanism. The company's product pipeline currently includes three product candidates in clinical trial stages: Accordion Pill Carbidopa/Levodopa, or AP-CD/LD, which is being developed for the treatment of Parkinson's disease symptoms in advanced Parkinson's disease patients, currently in phase III, Accordion Pill Zaleplon, or AP-ZP, which is being developed for the treatment of insomnia, including sleep induction and sleep maintenance, and an Accordion Pill that is being developed for the prevention and treatment of gastroduodenal and small bowel ulcers induced by nonsteroidal anti-inflammatory drugs. In addition, an Accordion Pill for cannabinoid therapies (AP-CBD/THC) will enter phase I clinical trial in the first quarter of 2017.

Positive Five-Year Clinical Data from Micell Technologies' MiStent Presented at TCT 2016

PRNewswire: October 31, 2016 – DURHAM, NC, U.S.A. – Micell Technologies, Inc. (Micell) today announced that it presented five-year clinical safety and efficacy results from the DESSOLVE I and II trials of its MiStent sirolimus eluting absorbable polymer coronary stent system (MiStent[®]). MiStent is designed to optimize vessel healing and long-term clinical performance in patients with coronary artery disease, and the presented data demonstrate sustained desirable clinical outcomes. These results were presented at the 28th Annual Transcatheter Cardiovascular Therapeutics (TCT) Conference. TCT, the world's largest educational meeting focused on interventional cardiovascular medicine, was held in Washington, D.C., October 29–November 2.

In a session titled "Emerging Bioresorbable Polymer-Based Metallic DES," five-year results were presented from the DESSOLVE I and II clinical studies, which demonstrated a combined (DES I and II) target lesion revascularization (TLR) rate of 2.7% at five years. No probable or definite stent thromboses were reported in either study through five-year follow-up. David E. Kandzari, M.D., director of interventional cardiology and interventional cardiology research for Piedmont Heart Institute of Atlanta, Georgia, made the presentation.

Dr. Kandzari commented, "These results from DESSOLVE I and II validate our initial hypothesis that MiStent's unique pharmacokinetic profile, with a rapidly absorbing polymer and extended elution of crystalline sirolimus, permits faster and stable vessel healing that translates to exceptional long-term outcomes."

Dean J. Kereiakes, M.D., medical director of the Christ Hospital Heart and Vascular Center and the Lindner Research Center, Cincinnati, Ohio, also presented data on the five-year results in a poster session. Dr. Kereiakes concluded, "This pooled analysis of patients treated with MiStent, which has a linear drug release and ultra-thin-strut, cobalt chromium stent design, suggests excellent long term safety and efficacy of this novel coronary stent."

Micell's patented supercritical fluid technology allows for a rigorously controlled coating of the drug and polymer, whereby the drug is applied to a bare-metal stent in a dry powder, crystalline form. This preserves its morphology and optimizes its pharmacokinetic (distribution and absorption) profile. MiStent also leverages the benefits of a cobalt chromium coronary stent system—a state-of-the-art, ultra-thin-strut metallic stent that has demonstrated excellent deliverability, conformability, and flexibility.

Dennis Donohoe, M.D., Micell's chief medical advisor, remarked, "MiStent uniquely provides continued vascular drug delivery for nine months—even after its bioresorbable polymer coating has been fully absorbed, which occurs over the course of 90 days." Dr. Donohoe continued, "Studies of MiStent to date have demonstrated a desirable lack of late lumen loss over 18 months, a characteristic that makes MiStent a clinically meaningful improvement in treating patients with coronary artery disease."

MiStent is designed to optimize healing and clinical performance in patients with coronary artery disease. The rapidly absorbable coating of MiStent, which contains crystalline drug (sirolimus) and an absorbable polymer, is intended to precisely and consistently provide for extended local drug delivery and limit the duration of polymer exposure. These characteristics potentially reduce the safety risks associated with currently commercially available drug-eluting stents and improve long-term clinical outcomes.

EU approval of MiStent was supported by clinical data from two studies, DESSOLVE I and II, which demonstrated superior in-stent late lumen loss rates and an excellent safety profile. Micell also completed enrollment in December 2015 of DESSOLVE III, a 1,400 patient, 20 center, randomized clinical trial comparing MiStent to Xience Everolimus Eluting Coronary Stent System[®] (Xience).

DESSOLVE III is a prospective, balanced, randomized, controlled, single-blind, multi-center study comparing clinical outcomes between MiStent and Xience in a "real world, all-comers" patient population. Patients in the trial suffered from symptomatic coronary artery disease, including those with chronic stable angina, silent ischemia, or acute coronary syndrome, and qualified for percutaneous coronary interventions. The primary endpoint for this trial is a non-inferiority comparison of target lesion failure (TLF) of the MiStent group versus the Xience group at 12 months post-procedure. The 12-month primary endpoint results for DESSOLVE III are expected to be released in the first half of 2017. MiStent has received CE marking, but is not approved for sale in the United States.

Aralez Completes Acquisition of Toprol-XL® and Its Authorized Generic from AstraZeneca

PRNewswire: October 31, 2016 – MISSISSAUGA, Ontario, Canada – Aralez Pharmaceuticals Inc. (NASDAQ: ARLZ) (TSX: ARZ), a global specialty pharmaceutical company, today announced that its subsidiary, Aralez Pharmaceuticals Trading DAC (Aralez Ireland), has completed its acquisition of the U.S. rights to Toprol-XL[®] (metoprolol succinate) and its authorized generic (AG) from AstraZeneca. In connection with the transaction, the parties entered into a supply agreement pursuant to which AstraZeneca will continue to manufacture and supply Toprol-XL and the AG to Aralez Ireland for at least ten years. AstraZeneca will also continue to distribute the product on behalf of Aralez Ireland until the product is transferred, which could be up to nine months following the closing under a transitional services agreement.

In accordance with the terms of the asset purchase agreement, the upfront amount of \$175 million was paid at closing. The transaction was financed through a previously committed senior secured debt facility with Deerfield Management. In addition to the \$175 million upfront payment to AstraZeneca, upon the closing of the transaction, Aralez borrowed funds under this credit facility to replenish \$25 million that was previously paid from cash on hand in connection with the recently completed ZONTIVITY[®] acquisition. In addition, Deerfield has agreed to provide Aralez access to up to an additional \$250 million in capital to fund future mutually agreeable acquisitions.

"We are pleased to announce the completion of the acquisition of the U.S. rights to Toprol-XL and its AG, which bolsters our position in the treatment of cardiovascular disease and significantly enhances our financial wherewithal with a more diversified revenue stream," said Adrian Adams, chief executive officer of Aralez. "The strong cash flow from the transaction is expected to accelerate our profitability to 2017 on an adjusted basis, while also offsetting launch costs for both YOSPRALA™ and ZONTIVITY. As a result of our strengthened financial profile following this transaction, together with the recent launch of YOSPRALA and planned relaunch of ZONTIVITY in 2017, we believe that we are nicely positioned drive long-term organic growth."

Toprol-XL is an extended-release tablet that belongs to a family of high blood pressure medications known as beta-blockers. Extended-release tablets need to be taken only once a day. After swallowing Toprol-XL, the coating of the tablet dissolves, releasing a

multitude of controlled release pellets filled with metoprolol succinate. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval of 24 hours.

Mati Therapeutics Expands Intellectual Property Portfolio

Business Wire: October 26, 2016 – AUSTIN, TX, U.S.A. – Mati Therapeutics, Inc. ("Mati") announced that it has been granted U.S. patent number 9,445,944 titled "Lacrimal Implants and Related Methods." The patent, which expires in 2028, claims a method of providing a sustained drug release to an eye using a proprietary punctal plug design placed in the punctum (tear duct) over the treatment period. This new patent complements earlier issued U.S. patent claims directed to the proprietary punctal plug for non-invasive sustained delivery of topical drugs to the eye. This proprietary technology is used for multiple disease states with consistent, sustained efficacy.

This newly issued patent further enhances Mati's patent portfolio, which includes more than 80 issued patents and numerous patent applications, to which Mati has exclusive rights in the United States and other major international markets. The patents cover 17 patent families, including important elements of the Evolute® punctal plug delivery system for treatment of ocular indications. The Evolute® platform includes features for retaining the punctal plug within the nasolacrimal system of the eye during drug elution and sustained release formulations currently in development for post-operative pain and inflammation.

"We continue to expand our international intellectual property portfolio consisting of 82 issued patents and 80 additional patent applications pending review," said Bob Butchofsky, CEO of Mati. "Mati continues to focus on innovation with our sustained drug delivery platform with the addition of 42 newly issued patents since 2014, covering the United States, Europe, Canada, Japan, and China. This is a key strategic asset for our company and will help support the multiple products we intend to develop with this unique sustained drug delivery platform."

Mati is developing the Evolute[®] sustained ocular drug delivery platform, which Mati believes has the potential to treat a range of ocular indications. The platform utilizes a device called a punctal plug, which is easily inserted into a patient's punctum. The device has already been approved to treat dry eye syndrome, but Mati is the first to conduct clinical trials in the United States, using punctal plugs as an anchoring device for a drug delivery platform. A drug-eluting core is inserted into Mati's proprietary punctal plug, which allows medication to be continuously released into the tear film of the eye over a period of time. Mati believes the Evolute[®] platform has the potential to become a more reliable alternative to several eye drop therapies, which can be ineffective because many patients are unwilling or unable to adhere to self-administered eye-drop regimens.

Mati has completed multiple phase II clinical trials using the Evolute[®] platform, including multiple trials in glaucoma, ocular hypertension, and allergy patients. Mati's proprietary punctal plug design has demonstrated excellent lower punctum retention rates of up to 92% and 96% over a 12-week follow-up period in multiple multi-center U.S. clinical trials. To learn more about Mati Therapeutics, visit www.MatiTherapeutics.com.

Braeburn Pharmaceuticals and Camurus Expand Collaboration and License Agreement to Include New Combination Product for Pain and Nausea

Business Wire: October 24, 2016 – STOCKHOLM, Sweden – Braeburn Pharmaceuticals and Camurus (STO: CAMX) today announced the expansion of their collaboration and license agreement from 2014 to include buprenorphine combination products. The first drug candidate within the expanded scope (CAM2058) is an extended release injectable combination of buprenorphine and granisetron in the FluidCrystal[®] injection depot technology. CAM2058 has completed formulation development and non-clinical evaluation and is being transferred to clinical development during the fourth quarter of 2016, initially being studied for the prevention and treatment of post-operative pain, nausea, and vomiting.

"We are pleased to announce this extension of our successful partnership with Camurus. This new product candidate has the potential to expand Braeburn's ability to offer relief across the continuum of post-operative pain management, including addressing the often co-occurring symptoms of nausea and vomiting," said Behshad Sheldon, president and CEO Braeburn Pharmaceuticals.

"We believe that CAM2058 has the potential to improve the wellbeing of patients post-surgery and reduce the need for other medications including oral opioid painkillers that are taken home and self-administered by the patient. The partnership with Braeburn Pharmaceuticals is a strong platform for the further global development of this new asset," said Fredrik Tiberg, president and CEO, Camurus. "CAM2058 combines these two treatment modalities in a single, small volume, sustained release injection that is made possible by using our FluidCrystal[®] technology."

"Postoperative pain, nausea, and vomiting are real management concerns for patients and their physicians. The concept of CAM2058 combining prolonged pain relief with prophylactic and sustained treatment of nausea and vomiting is unique. The opportunity to manage these conditions during the critical post-operative phase with a single injection is a compelling proposition for both patients and treatment providers," said Andrea Barthwell, MD, DFASAM, addiction specialist, whose practice includes pain management.

Effective postoperative pain management is an indispensable component of the continuum of care for the surgical patient. Inadequate pain control may result in delayed mobilization and recovery, pulmonary and cardiac complications, and an increased likelihood of the development of neuropathic pain. Data available indicate that opioid therapy together with neural blockade is among the most effective treatments of postoperative pain. Given its safety and efficacy profile when compared to full opioid agonists (e.g., morphine, oxycodone, and fentanyl), buprenorphine should be considered for first line therapy for the treatment of a wide range of acute as well as chronic pain conditions. Ideal buprenorphine formulations would deliver rapid onset and persistent plasma levels for extended duration as mono or combination therapy. The advantages of effective pain management include better patient comfort, satisfaction, and earlier mobilization, which together with a faster recovery may reduce cost of care.

CAM2058 consists of a combination buprenorphine and granisetron subcutaneous extended release injection product in development for the potential treatment of post-operative as well as other pain indications. The unique properties of the FluidCrystal technology allow for the durations that are specifically tailored to the target application, allowing for both shorter and longer-term treatments. CAM2058 is designed for low volume subcutaneous injection by healthcare personnel to ensure proper delivery while reducing the need for take home medication that are often associated the risk of diversion, abuse, and misuse.

Braeburn Pharmaceuticals, an Apple Tree Partners company, is a commercial stage pharmaceutical company delivering individualized medicine in neuroscience. Long-acting therapeutic treatment options can be essential to improving patient outcomes and facilitating recovery in neurological and psychiatric disorders, which are often complicated by stigma and present significant public health challenges. Probuphine, Braeburn's long-acting buprenorphine implant, was approved by the FDA in May 2016. Braeburn's investigational product pipeline consists of long-acting implantable and injectable therapies for serious neurological and psychiatric disorders, including opioid addiction, pain, and schizophrenia. Braeburn's pipeline products are at various stages of clinical development and include CAM2038, weekly and monthly subcutaneous injection depot formulations of buprenorphine, being investigated in opioid addiction and pain and a risperidone six-month implant being investigated in schizophrenia. More information on Braeburn can be found at www.braeburnpharmaceuticals.com.

Camurus is a Swedish research-based pharmaceutical company committed to developing and commercializing innovative and differentiated medicines for the treatment of severe and chronic conditions. New drug products with best-in-class potential are conceived based on the proprietary FluidCrystal[®] drug delivery technologies and an extensive R&D expertise. Camurus' clinical pipeline includes products for treatment of cancer, endocrine diseases, pain, and addiction, developed in-house and in collaboration with international pharmaceutical companies. The company's share is listed on Nasdaq Stockholm under the ticker "CAMX." For more information, visit www.camurus.com.

Ocular Therapeutix[™] and Regeneron Enter into Strategic Collaboration to Develop Sustained Release Formulation of Aflibercept for the Treatment of Wet AMD and Other Serious Retinal Diseases

Business Wire: October 13, 2016 – BEDFORD, MA, U.S.A. – Ocular Therapeutix, Inc. (NASDAQ: OCUL), a biopharmaceutical company focused on the development and commercialization of innovative therapies for diseases and conditions of the eye, today announced that it has entered into a strategic collaboration, option and license agreement with Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN). Ocular and Regeneron will collaborate on the development of a sustained release formulation of the vascular endothelial growth factor (VEGF) trap aflibercept for the treatment of wet age-related macular degeneration (wet AMD) and other serious retinal diseases. This formulation is currently in preclinical development. Regeneron's aflibercept is currently approved by the U.S. Food and Drug Administration for certain indications under the brand name EYLEA*.

Ocular Therapeutix is currently developing proprietary sustained-release hydrogel-based drug delivery depots for intravitreal injection that can be formulated with both small and large molecule pharmaceuticals, such as tyrosine kinase inhibitors (TKIs) and proteinbased anti-VEGFs, respectively, with the goal of delivering sustained and therapeutic levels of drugs to targeted ocular tissues. Under the terms of the agreement, Ocular Therapeutix and Regeneron will aim to develop a sustained release formulation of aflibercept that is suitable for advancement into clinical development. Regeneron has the option to obtain an exclusive license to use Ocular Therapeutix's hydrogel-based technology for the development and commercialization of a sustained release formulation of aflibercept and other biologics targeting VEGF for ophthalmic indications. Ocular Therapeutix will retain all rights to develop its sustained-release hydrogel-based drug delivery platform with all other non-VEGF targeting compounds as well as with small molecule pharmaceuticals, including TKIs, for other retinal diseases.

Upon exercising of the option, Ocular Therapeutix would receive a payment of \$10 million from Regeneron, and Ocular Therapeutix would be responsible for funding development through phase 1. Regeneron would be responsible for any subsequent development and commercialization costs. Ocular Therapeutix would be eligible to receive up to \$305 million in milestone payments from Regeneron for a sustained release version of aflibercept containing Ocular Therapeutix's sustained release hydrogel depot, comprising up to \$155 million in development and regulatory milestone payments, \$100 million for the first commercial sale and up to \$50 million in commercial milestone payments. In addition, Ocular Therapeutix is eligible to receive tiered high single-digit to low-to-mid teen-digit royalties on potential future net sales.

"We have made considerable progress in developing our protein drug delivery platform at Ocular Therapeutix, so it is good to see an industry leader such as Regeneron recognizing the potential of this technology," said Amar Sawhney, Ph.D., president, chief executive officer, and chairman of Ocular Therapeutix. "We are excited to partner with Regeneron to develop a potential first-in-class sustained release protein-based anti-VEGF hydrogel injection for wet AMD, DME, RVO, and other serious retinal diseases. This sustained release formulation could have the potential to significantly reduce dosing frequency and subsequently reduce doctor visits, thus reducing the burden of care for patients, caregivers, and physicians, and may decrease the likelihood of certain side effects associated with frequent intravitreal injections."

Wet age-related macular degeneration (wet AMD) is characterized by loss of vision caused by degeneration of the central portion of the retina. Abnormal growth of blood vessels below the retina, and the leakage of fluid and protein from the vessels, causes retinal degeneration and can lead to severe and rapid loss of vision. Wet AMD is the leading cause of blindness in individuals aged 50 years or older.

Retinal vein occlusion (RVO) is a sight-threatening disorder resulting from the blockage of one of the veins carrying blood out of the retina. In RVO, the blockage of a retinal vein can lead to poor blood circulation, low oxygen, and sometimes inflammation in the eye. A blocked vein will leak its contents of blood and fluid. Bleeding within the retina and swelling from the fluid can result in macular edema.

Diabetic macular edema (DME) is a complication of diabetes caused by fluid accumulation in the macula, or central portion of the eye. When the macula begins to fill with fluid, the ability of those cells to sense light is impaired, causing blurred vision that can be severe. Diabetic macular edema affects up to 30% of people who have had diabetes for 20 years or more, and if untreated, 20 to 30% of people who have it will experience moderate visual loss. The global market for anti-VEGF drugs is over \$7.5 billion.

Ocular Therapeutix, Inc. (NASDAQ: OCUL) is a biopharmaceutical company focused on the development and commercialization of innovative therapies for diseases and conditions of the eye using its proprietary hydrogel platform technology. Ocular Therapeutix has submitted an NDA for post-surgical pain for its lead product candidate, DEXTENZA[™] (dexamethasone insert, extended release), which is in phase 3 clinical development for post-surgical ocular inflammation and pain and allergic conjunctivitis and in phase 2 clinical development for dry eye disease. OTX-TP (sustained release travoprost) is in phase 3 clinical development for glaucoma and ocular hypertension. Ocular Therapeutix is also evaluating sustained-release injectable drug depots for back-of-the-eye diseases. Ocular Therapeutix's first product, ReSure[®] sealant, is FDA-approved to seal corneal incisions following cataract surgery. For additional information about the company, please visit www.ocutx.com.

Plant-Made Biopharmaceuticals Target Dental Plaque, Gum Tissues

PRNewswire: October 10, 2016 – PHILADELPHIA, PA, U.S.A. – Biopharmaceuticals like insulin have been used for decades in medical practice, but dental medicine has few such drugs and those that are used are delivered invasively, often through gum surgery.

Now, a report in *Biomaterials* by Penn Dental Medicine's Dr. Michel Koo and Dr. Henry Daniell suggests a new approach for delivering a biopharmaceutical to treat and prevent oral diseases, including dental caries (cavities). Caries predominantly affect children and adults of lower socioeconomic status and account for over \$40 billion in health-care spending annually.

Using plants to produce antimicrobial peptides, the researchers were able to kill tooth-decay-causing bacteria and thwart their ability to form biofilms on a tooth-like surface with a single topical treatment. The peptides were even more effective when combined with an enzyme that degrades the matrix that surrounds bacteria inside biofilms. They also demonstrated that these peptides could be taken up by gingival cells.

The platform is low-cost compared to the current means of producing biopharmaceuticals and presents a unique opportunity to develop an affordable therapeutic approach that simultaneously attacks disease-causing plaque and promotes gum health.

To address the prohibitive cost of antimicrobial peptide production, the researchers turned to Daniell's plant-based drug production platform. It entails bombarding a plant leaf with a cloned gene of interest to reprogram the chloroplasts to synthesize the associated protein. In this case, they coaxed plants to produce two antimicrobial peptides, retrocyclin and protegrin. Both peptides have complex secondary structures, making them expensive to produce by traditional means. But the researchers found they could literally grow them in Daniell's greenhouse and replicate their unique secondary structures in the plant's leaves.

Koo's lab tested whether the plant-made agents could prevent biofilm creation. They exposed a saliva-coated tooth-like surface to the plant-made protegrin for 30 minutes, then exposed the surface to *S. mutans* cells along with sugar, and found that it significantly impaired the ability of the bacterium to form a biofilm compared to an untreated surface.

To see whether the antimicrobials could also act therapeutically, they next exposed a pre-formed biofilm on the tooth-mimicking surface to either protegrin alone or a combination of protegrin and a matrix-degrading enzyme. The combination was powerful—able to degrade 60% of the matrix and killing even more bacteria than the antimicrobial alone.

Beyond topical-drug delivery, Daniell's lab has been investigating molecular "tags" to route protein drugs to human cells to treat several diseases. In this context, delivering growth hormones or other such drugs to gum tissues for wound healing or bone regeneration is of paramount importance to enhance oral health. Their study found that the plant-made antimicrobial peptides could be taken up by human cells in the oral cavity.

"This opens up a completely new field for drug delivery with a topical agent," Daniell said.

A collaboration with Johnson & Johnson Consumer Inc. will enable Koo and Daniell to continue optimizing their antimicrobialenzyme production system. One possibility, they note, is a chewing gum laced with antimicrobial peptides that could slowly release as one chews.

Lupin and MonoSol Rx Announce Licensing Agreement for Multiple Pediatric-Focused Products

PRNewswire: October 6, 2016 – WARREN, NJ, U.S.A., BALTIMORE, MD, U.S.A., and MUMBAI, India – Lupin Pharmaceutical Inc., the U.S. subsidiary of pharma major Lupin Limited (collectively Lupin), and MonoSol Rx, a specialty pharmaceutical company, have entered into a strategic licensing agreement wherein Lupin would develop multiple pediatric products utilizing MonoSol Rx's proprietary PharmFilm[®] drug delivery technology.

MonoSol Rx's PharmFilm[®] technology is a drug delivery platform that provides precision dosing in the form of a quick-dissolving, taste-masked, and easy-to-administer dissolvable film. MonoSol Rx is a global leader in film-based drug delivery applications with two FDA-approved products and a robust pipeline of pharmaceuticals in development. For patients who may have difficulty swallowing pills or tolerating medication in traditional delivery forms, PharmFilm[®] technology provides a minimally invasive alternative to pills, injections, and gels, with the goal of helping patients adhere to their prescribed treatment regimens in order to improve their health. The technology could offer potential to support pediatric patients in particular, many of whom have difficulty with the currently available oral or injectable dosing of needed medications.

"We believe PharmFilm[®] technology holds great promise for pediatric applications—enabling increased compliance and adherence in a difficult to treat population," said Keith J. Kendall, CEO, MonoSol Rx. "By partnering with Lupin, whose commitment to support and expand within the pediatric and family-focused market matches our own commitment to helping pediatric patients and their families, we are taking a critical step forward in developing valuable and much-needed products."

As an innovation-led, transnational pharmaceutical company developing a wide range of branded and generic formulations, Lupin is known for its commitment to, and successful track record of, improving accessibility, patient experience, and addressing unmet medical needs globally. The agreement would be in line with the company's focus on expanding into the specialty pharmaceutical market, and specifically, pediatric needs such as attention-deficit/hyperactivity disorder (ADHD).

"At Lupin, we are motivated by addressing urgent, unmet medical needs—and helping children and their families ensure they are able to access, tolerate, and successfully take the medicines they need is a clear part of that mission," said Paul McGarty, president, Lupin Pharmaceuticals. "Our alliance with MonoSol Rx will enable us to expand our family of pediatric products to help meet the needs of children for a variety of indications. We look forward to working with MonoSol Rx on the development of these products."

MonoSol Rx is a specialty pharmaceutical company leveraging its proprietary PharmFilm® drug delivery technology to develop products that improve patient outcomes and address unmet needs. These pharmaceutical and over-the-counter products are developed

independently and with partners. PharmFilm can provide a benefit to patients by improving the efficacy, safety, and convenience of currently marketed pharmaceutical products, new molecular entities, and combination products. MonoSol Rx's leadership in film drug delivery is supported by strong IP protection, a robust pipeline of prescription drug formulations, and two FDA-approved products—Suboxone[®] (buprenorphine and naloxone) sublingual film and Zuplenz[®] (ondansetron) oral soluble film. For press releases and other company information, please visit www.monosolrx.com.

Headquartered in Baltimore, Maryland, Lupin Pharmaceuticals, Inc., is dedicated to delivering high-quality, branded and generic formulations trusted by healthcare professionals and patients in the United States. LPI entered the United States in 2004 and has since evolved as a market leader in generics and specialty pediatric treatments with new generic and brand products that improve on existing treatments, seek to fulfill unmet needs and improve patient experience. LPI is the 5th largest pharmaceutical company in the United States by prescriptions (4.68% market share—IMS Health, National Prescription Audit, March 2016). For more information on LPI, please visit www.lupinpharmaceuticals.com.

Lupin is an innovation led transnational pharmaceutical company developing and delivering a wide range of branded and generic formulations, biotechnology products, and APIs globally. The company is a significant player in the cardiovascular, diabetology, asthma, pediatric, CNS, GI, anti-infective, and NSAID space and holds global leadership position in the anti-TB segment.

Lupin is the 5th and the 7th largest generics pharmaceutical company by market capitalization and sales globally (March 31, 2016, Bloomberg). The company is the 5th largest pharmaceutical player in the United States by prescriptions (4.68% market share—IMS Health, National Prescription Audit, March 2016); the 3rd largest Indian pharmaceutical company by revenues; the 6th largest generic pharmaceutical player in Japan; and the 4th largest generic pharmaceutical company in South Africa (IMS Health, March 2016).

For the financial year ended March 31, 2016, Lupin's consolidated sales and net profit stood at Rs. 136,539 million (USD 2.09 billion) and Rs. 22,607 million (USD 345 million), respectively. Please visit www.lupin.com for more information.

September

Dicerna Prioritizes Resources to Advance GalXC™ Product Candidates

Business Wire: September 26, 2016 – CAMBRIDGE, MA, U.S.A. – Dicerna Pharmaceuticals, Inc. (Nasdaq:DRNA), a leading developer of investigational RNA interference (RNAi) therapeutics, today announced that the company will focus its resources on its proprietary GalXC[™] technology platform to advance development of product candidates in its core therapeutic areas of rare diseases, chronic liver diseases, cardiovascular disease, and viral infectious diseases. Under this plan, Dicerna will transition its primary hyperoxaluria (PH) development program to focus on DCR-PHXC, a subcutaneously delivered GalXC clinical candidate, which was announced earlier this year. The company also announced that it will discontinue clinical development of DCR-MYC, a DsiRNA-based therapeutic formulated as an EnCore[™] lipid nanoparticle (LNP) for delivery to solid tumors, because preliminary results do not meet the company's expectations for further development.

"Based on the performance of the GalXC platform, the strength of the preclinical data, and the broad therapeutic opportunities for RNAi in liver-targeted diseases, we are prioritizing resources to advance the product candidates emerging from this platform," said Douglas M. Fambrough, Ph.D., president and chief executive officer of Dicerna. "Discontinuing our DCR-PH1 and DCR-MYC lipid nanoparticle programs allows us to focus our resources on efficiently developing our GalXC product candidates and building on the solid scientific foundation in RNAi that Dicerna has developed over the past decade. We greatly appreciate the participation of all of the patients, families, and clinical investigators in the DCR-PH1 development program, as their contributions provided important insights into the primary hyperoxaluria disease state, which will guide the development of DCR-PHXC."

The GalXC platform is a fully enabled RNAi drug discovery engine with potentially powerful capabilities that the company believes could result in potency that is on par with or better than comparable platforms. As Dicerna reported during its recent investor day, subcutaneously delivered GalXC compounds silenced 12 different disease targets in animal models, highlighting the long duration of action, infrequent dosing, and tolerability of GalXC-based compounds. Use of the GalXC platform yielded gene silencing of greater than 90% for multiple genes in non-human primates (NHPs) after a single dose. In an NHP model of an undisclosed rare disease gene target, a single 3 mg/kg dose achieved a maximum gene silencing of 94%, with an average gene silencing of approximately 88%. Another single 3 mg/kg dose NHP study resulted in an average of 97% silencing of an undisclosed rare disease gene target. Based on this evidence, Dicerna believes that DCR-PHXC has the potential to be a new treatment option for patients with PH.

In addition to DCR-PHXC, which is in preclinical development, Dicerna expects to launch two more GalXC programs in 2016: one will focus on cardiovascular disease targeting PCSK9; the other is an undisclosed rare disease program. Dicerna expects to launch three additional programs annually, with the intent to advance five programs into the clinic by 2019.

GalXC compounds offer several unique characteristics, including:

- Longer RNAi duplexes (i.e., compared to standard RNAi molecules) provide greater potential to increase potency and reduce toxicity, using a toolbox of standard oligonucleotide chemistries.
- A unique tetraloop configuration stabilizes the RNA duplex, provides multiple points for addition of GalNAc sugars, and interfaces effectively with the RNAi machinery within target cells.
- The GalXC platform enables rapid discovery and efficient advancement of research activities. Within 30 days of nominating a gene target, Dicerna can design, synthesize, and validate an *in vivo* GalXC construct.

Dicerna will transition its PH development program to focus on DCR-PHXC and expects to file an IND or CTA for DCR-PHXC in late 2017. The company will discontinue the development program for DCR-PH1, an investigational therapy formulated in an LNP delivery system obtained through a licensing agreement with Arbutus Biopharma Corporation (formerly known as Tekmira Pharmaceuticals Corporation). DCR-PH1 was being studied in two clinical trials, DCR-PH1-101 in patients with primary hyperoxaluria type 1 (PH1) and DCR-PH1-102 in normal healthy volunteers (NHVs).

Data from the DCR-PH1-102 clinical trial, in which 21 NHVs were randomized to receive DCR-PH1 at a dose of 0.005, 0.015, and 0.05 mg/kg or placebo, showed an increase in urine glycolate levels, a biomarker of DCR-PH1 treatment activity, in the top two DCR-PH1 dosing groups. Those data, which were presented on September 22, 2016, at the 17th Congress of the International Pediatric Nephrology Association in Iguaçu, Brazil, provide the proof of concept for the pharmacological activity of RNAi-based therapy in PH. Based on the DCR-PH1 proof-of-concept data in humans, the utility of the GalXC platform, and the DCR-PHXC preclinical data, the company believes DCR-PHXC has the potential to be a better therapeutic candidate for patients with PH.

"The encouraging data from Dicerna give us hope that research on a GalXC-based therapeutic agent can potentially benefit patients living with primary hyperoxaluria, a devastating disease that often causes early-onset renal failure," said Craig Langman, M.D., a pediatric nephrologist and the Isaac A. Abt, M.D., professor of kidney diseases at the Feinberg School of Medicine, Northwestern University and head, kidney diseases, at Lurie Children's Hospital. "There is a significant unmet medical need for a viable therapy for patients with primary hyperoxaluria, as the current treatment option consists of combined transplantation of the kidney and liver, a highly invasive procedure with significant morbidity."

As a part of the company's ongoing commitment to the PH1 community, Dicerna will continue to advance its Primary HYperoxaluria Observational Study (PHYOS), which is collecting data on key biochemical parameters implicated in the pathogenesis of PH1. The company hopes to use these data to better understand the baseline PH1 disease state, knowledge that will help guide long-term drug development plans.

"We look forward to continuing to work with Dicerna as the company investigates a potential therapeutic option for the PH community, and we appreciate the company's decision to move forward with a new investigational therapy based on recent scientific advances," said Kim Hollander, executive director of the Oxalosis and Hyperoxaluria Foundation. "We encourage patients and families affected by PH to learn more about clinical trials and international patient registries, which we hope will strengthen our understanding of PH for potential therapies in the future."

Dicerna will discontinue the clinical development program for DCR-MYC, which was being investigated in two clinical trials: DCR-MYC-101, a phase 1 trial in patients with advanced solid tumors and hematological malignancies, including an expansion cohort in patients with pancreatic neuroendocrine tumors; and DCR-MYC-102, a phase 1b/2 trial in patients with advanced hepatocellular carcinoma (HCC). MYC is an oncogene frequently amplified or overexpressed in a wide variety of tumor types. While preliminary data from the DCR-MYC-101 trial provided evidence of clinical response and molecular knockdown of MYC in patients, the early efficacy results do not meet the company's expectations to warrant further development. Paired tumor biopsies preand post-treatment showed proof of concept with drug delivery and provided clear evidence of RNAi-mediated MYC messenger RNA destruction in tumors from all patients tested; however, the level of MYC knockdown was below the level of molecular knockdown that the company targeted. In the HCC trial, topline findings showed that a dose of up to 0.85 mg/kg was well tolerated; however, no clinical activity (based on the modified response evaluation criteria in solid tumors criteria) has been observed to date. In addition to DCR-MYC, Dicerna has a second oncology program, DCR-BCAT, which targets the WNT-beta-catenin pathway.

Given the company's focus on advancing its GalXC-based programs, Dicerna will seek strategic alternatives to further develop DCR-BCAT, which employs an improved and enhanced EnCore LNP delivery capability, compared to earlier versions of the technology.

GalXC[™] is a proprietary technology platform invented by Dicerna to advance the evaluation of next-generation RNAi-based therapies designed to silence disease-driving genes in the liver. Compounds produced via the GalXC technology are intended to be broadly applicable across multiple therapeutic areas, including rare diseases, chronic liver diseases, cardiovascular disease, and viral infectious diseases. Using GalXC, Dicerna scientists attach *N*-acetylgalactosamine (GalNAc) sugars directly to the extended region of a Dicer substrate short-interfering RNA (DsiRNA-EX) molecule, yielding multiple proprietary conjugate delivery configurations. GalXC enables subcutaneous delivery of Dicerna's RNAi therapies to hepatocytes in the liver, where they are designed to specifically bind to receptors on target cells, potentially leading to internalization and access to the RNAi machinery within the cells. The technology may offer several distinct benefits, as suggested by strong preclinical data. These benefits include potency that is on par with or better than comparable platforms; highly specific binding to gene targets; long duration of action; and an infrequent dosing regimen. Conjugates produced via the GalXC platform can be administered as simple saline solutions and do not need transport technologies (such as lipid nanoparticles) to facilitate delivery.

Dicerna Pharmaceuticals, Inc., is an RNA interference-based biopharmaceutical company focused on the discovery and development of innovative treatments for rare, inherited diseases involving the liver and for other therapeutic areas in which the liver plays a key role. The company is using its proprietary RNA interference (RNAi) technology platform to build a broad pipeline in these therapeutic areas. In many cases, Dicerna is pursuing targets that have historically been difficult to inhibit using conventional approaches but where connections between targets and diseases are well understood and documented. The company intends to discover, develop, and commercialize these novel therapeutics either on its own or in collaboration with pharmaceutical partners. For more information, please visit www.dicerna.com.

Bristol-Myers Squibb Awards First "Golden Tickets" for LabCentral to PanTher, Suono Bio

Business Wire: September 20, 2016 – NEW YORK, NY and CAMBRIDGE, MA, U.S.A. – Bristol-Myers Squibb Company (NYSE: BMY) and LabCentral, an innovative, shared laboratory space designed as a launch pad for life-sciences and biotech startups, today announced that PanTher and Suono Bio are the winners of Bristol-Myers Squibb's Golden Tickets for LabCentral. As a platinum sponsor of LabCentral, Bristol-Myers Squibb can select up to two innovative life-sciences and biotech startup companies per year of active sponsorship for "Golden Tickets," which underwrite the cost of one lab bench for one year in LabCentral's Kendall Square facility.

"PanTher and Suono Bio are working to deliver innovative technologies that have the potential to impact patients with serious diseases, and we're pleased that the Golden Tickets will enable them to advance their research," said Carl Decicco, Ph.D., head of discovery at Bristol-Myers Squibb. "Our sponsorship of LabCentral, and the awarding of Golden Tickets to these two companies, align with our strategy to encourage scientific innovations in our disease areas of focus, from academia through early development."

"Bristol-Myers Squibb has made an excellent selection of its first two Golden Ticket winners—we know them both well," commented LabCentral co-founder and president Johannes Fruehauf, M.D., Ph.D. "Both have the potential to make major inroads against devastating diseases using novel approaches to drug delivery. We are excited to have them join in the vibrant ecosystem of the LabCentral community and look forward to watching as these companies move down the path toward success."

A pre-clinical-stage company, PanTher Therapeutics is working to revolutionize the treatment of inoperable, locally advanced solid tumors—studying the direct delivery of existing, already proven chemotherapy agents directly onto the tumor for consistent, slow release over time. The company designed its novel delivery method to potentially eliminate the toxicity and debilitating side effects that chemo agents can produce when delivered systemically through traditional IV or oral administration. Its first potential indication is pancreatic cancer, a particularly lethal disease that affects more than 53,000 Americans annually, where excruciating symptoms arise from the primary mass invading nearby vital organs. By changing the route of administration to target just the tumor, PanTher is designed to increase the amount of drug reaching the intended destination with the aim to enhance therapeutic efficacy. Eliminating adverse outcomes may also help to lower healthcare costs. Pancreatic cancer accounts for about 3% of all cancers in the United States and about 7% of cancer deaths. A privately held company, PanTher is completing pre-clinical studies prior to initiating human trials and exploring opportunities for partnerships to expand its product pipeline.

Suono Bio, a preclinical stage company, has developed breakthrough technology—the "SuonoCalm™" system—designed to potentially enable ultra-rapid delivery of therapeutics across tissues, including the gastrointestinal (GI) tract. Preclinical studies have demonstrated that the ultrasound-based technology can deliver small molecules, proteins, and nucleic acids locally and systemically, validating further

study of the SuonoCalm system. Designed as an easy-to-use device to enable patients to self-administer medication at home, the SuonoCalm technology may also be applicable to a broad set of conditions outside of the GI tract.

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop, and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube, and Facebook.

A 28,000 square-foot facility in the heart of the Kendall Square, Cambridge, Massachusetts, a biotech innovation hub, LabCentral (www.labcentral.org; twitter @labcentral) is a first-of-its-kind shared laboratory space designed as a launchpad for high-potential lifesciences and biotech startups. It offers fully permitted laboratory and office space for early-stage companies comprising approximately 125 scientists and entrepreneurs. LabCentral provides first-class facility and administrative support, skilled laboratory personnel, a domain-relevant expert speaker series—as well as the other critical services and support that startups need to begin laboratory operations on day one. A private, nonprofit institution, LabCentral was funded in part by a \$5 million grant from the Massachusetts Life Sciences Center, with support from its real-estate partner, MIT. Founding sponsors include Triumvirate Environmental and Johnson & Johnson Innovation.

Transdermal Delivery Solutions and ALZYN Announce License for HypoSpray® Delivery of Alzheimers Therapy

Business Wire: September 20, 2016 – PALM BEACH GARDENS, FL, U.S.A. – Transdermal Delivery Solutions Corporation (TDSC) announced today the signing of a product license arrangement with ALZYN, LLC, of St. Petersburg, Florida.

"We are pleased to announce the finalization of our agreement for this product with the team at ALZYN," said Kenneth Kirby, president of TDSC.

ALZYN is a development stage company pursuing a unique approach to retard the progression of Alzheimer's disease employing well-characterized compounds that were licensed from the Florida State Research Foundation. This new and novel approach was developed by Dr. Ewa Bienkiewicz, research associate professor and director of the Protein Biology Laboratory at Florida State University's College of Medicine. She selected and tested several compounds, demonstrating their efficacy in a proof-of-concept study. She and her team evaluated levels of several diverse biomarkers associated with Alzheimer's disease. These markers are believed to drive the cascading symptoms of AD as it progresses. Collectively, the observed modifications in AD pathology biomarkers reflected a promising therapeutic breakthrough and preventive strategy to combat this disease. Dr. Bienkiewicz's findings have been accepted for peer-reviewed publication in a leading journal. "Dr. Bienkiewicz's studies are very encouraging," said ALZYN managing director Don Rosenkoetter. "The prospect of moving this science from the lab to the people who so desperately need a safe and efficacious therapy that will alter the course of this tragic disease engenders a tremendous passion and energy amongst our team. In TDSC and Langford Research Institute we have found development partners that both have the capabilities we were seeking and share our sense of urgency and mission."

While these compounds are showing great promise in validated *in vitro* experiments, dosing is a challenge. The digestive tract very effectively digests these compounds so creating a concentration high enough to be effective against the AD beta amyloid peptides in the brain is our mission. The HypoSpray technology transdermally bypasses the digestive tract and enables raising effective dose levels of these compounds. TDSC and its affiliated research arm, the Langford Research Institute, will formulate a spray-on solution that is expected to create the blood and brain levels documented in studies of the individual compounds to be effective. The formula will be tested first for proof of concept and for dose levels in patients. "This use of the HypoSpray technology to enable therapeutic outcomes with these compounds by means of a transdermal formulation is a significant step for biotechnology compound dosing," Kirby stated.

TDSC is committed to advancing the science of transdermal drug delivery using its patented spray-on delivery system. TDSC's proprietary system enables medications to be delivered directly through the skin, for systemic or localized application, utilizing its rapid acting, patchless, spray-on technology. No other company can offer similar, consumer friendly, dosing flexible solutions. www.youtube.com/watch?v=Ff-1z1SYoF8 Visit: www.tdsc.us

ALZYN is an early stage company committed to reducing the tragedy of Alzheimer's. The company is pursuing a unique and promising approach to halting the progression of AD. The science, licensed from the Florida State Science Foundation, is at a preclinical development stage. ALZYN is being advised by the Newport Board Group.

LRI is a South Florida-based not-for-profit institute dedicated to supporting the research of TDSC and its affiliates and partners. The institute is a U.S. FDA-registered drug labeler, U.S. DEA controlled substance researcher and exporter, an NIH registered facility,

and a State of Florida licensed pharmaceutical manufacturer. The institute is a cGMP facility approved to manufacture clinical trial materials. www.Langfordresearch.org

Aphios to Develop HIV/AIDS Cure Using Combination Drugs in Targeted "Nanosomes" Nanoparticles

Business Wire: September 13, 2016 – WOBURN, MA, U.S.A. – Aphios Corporation today announced that it plans to continue its research to develop a cure for HIV/AIDS using combination drugs in targeted "nanosomes" nanoparticles with recent funding from the National Institute of Allergy and Infectious Diseases (NIAID), NIH.

Currently, about 35 million people have died from AIDS, and there are about 37 million people living with HIV/AIDS worldwide. In the United States, an estimated 1.2 million people are currently living with HIV and more than 40,000 new infections occur each year. There is no vaccine against HIV, and AIDS, if untreated, will lead to the death of over 95% of infected individuals 10 years post-infection. HIV infects several cell types during the course of infection and progression to acquired immune deficiency syndrome (AIDS). The persistence of latent HIV-infected cellular reservoirs represents the remaining major hurdle to virus eradication with current anti-retroviral therapy (cART), since latently infected cells remain a permanent source of viral reactivation. It has been hypothesized that intensification of cART could reduce the residual viremia, but recent studies strongly suggest that this is not a likely scenario. Moreover, cART is problematic because of long-term toxicity, drug resistance, accelerated immune system aging, and the inability to target and eliminate persistent viral reservoirs. Therefore, other pharmacological approaches targeting the HIV-1 reservoir have been suggested by several investigators as a promising strategy to develop new drugs able to activate latent HIV-1 without inducing global T cell-activation.

According to Dr. Trevor P. Castor, CEO and principal investigator on this research, "We plan to develop a unique combination therapy consisting of a protein kinase C (PKC) modulator and a histone deacetylase (HDAC) inhibitor in nanosomes to reactivate these latent HIV reservoirs so that HIV-1 can be eliminated by the body's own immune system and/or cART and thus eradicated from the patient's body. We plan to deliver these drugs to their targets at the same time using targeted, immunologically spiked 'nanosomes' nanoparticles." The research will be conducted by a multidisciplinary team of scientists and engineers with advise and support from Dr. Robert F. Siliciano, M.D., Ph.D., professor of medicine, Johns Hopkins University School of Medicine, and investigator, Howard Hughes Medical Institute, who will also provide support with respect to the *ex vivo* evaluation of the combination PKC-HDACi nanosomes; Dr. Eduardo Munoz, M.D., Ph.D., professor of immunology, University of Cordoba, Spain, an HIV latency researcher and scientific advisor to Aphios Corporation; Dr. Santiago Moreno, M.D., head, infectious diseases, Ramón y Cajal Hospital, and professor of infectious diseases, University of Alcalá, Madrid, Spain, an HIV clinician and principal investigator of a recently completed phase I/ IIa clinical trial of a PKC modulator for HIV latency in HIV patients on cART in Spain; and Dr. Joseph L. Bryant, D.V.M., director, Division of Animal Models, Institute of Human Virology, and associate professor, Department of Pathology, University of Maryland School of Medicine, an HIV animal model expert, who will lead the *in vivo* toxicity and efficacy animal studies planned. Dr. Castor continued, "Our approach has the potential for advancing HIV therapy towards a sterilizing cure, which currently is out of reach of the HIV/AIDS community."

Aphios (www.aphios.com) is a clinical stage biotechnology company developing green enabling technology platforms to improve drug discovery, manufacturing, nanotechnology drug delivery, and pathogenic safety and, based on these platforms, enhanced therapeutics to improve quality of life and treat chronic diseases such as prostate and pancreatic cancers, infectious diseases such as HIV/AIDS, and central nervous system disorders such as Alzheimer's disease and multiple sclerosis in an environmentally sustainable manner. Research reported in this press release is supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health under Award Number R43AI124819. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Catalent to Acquire Pharmatek, Adding Expanded Drug Development Services and Spray Drying Technology

Business Wire: September 13, 2016 – SOMERSET, NJ, U.S.A. – Catalent, Inc. (NYSE: CTLT), the leading global provider of advanced delivery technologies and development solutions for drugs, biologics, and consumer health products, today announced an agreement for Catalent, through its wholly owned subsidiary, Catalent Pharma Solutions, Inc., to acquire Pharmatek Laboratories, Inc., a West Coast, U.S.-based specialist in drug development and clinical manufacturing. The acquisition will add extensive early-phase drug development capabilities from discovery to clinic, bring spray drying into Catalent's portfolio of drug formulation and delivery technologies, and expand Catalent's capability for handling highly potent compounds. The addition of spray drying will also provide Catalent customers with a comprehensive suite of bioavailability enhancement solutions, while complementing and expanding Catalent's OptiForm[®] solution suite platform, a science-driven parallel screening approach to identify the optimal formulation pathway for poorly soluble compounds. No financial details have been disclosed.

Founded in 1999, Pharmatek provides dosage form development and clinical-scale cGMP manufacturing of oral, injectable, and topical products for more than 100 customers globally. At its San Diego facility, Pharmatek offers a fully integrated drug development platform, with discovery formulation screening for lead selection and optimization, comprehensive formulation development and analytical services, and finished dose form manufacturing for clinical supply. Additional services include first-in-man strategies, solutions for poorly soluble compounds, controlled release formulations, and specialized facilities and controls for potent compound handling.

"Catalent continues to expand its industry-leading drug development and delivery technologies to help its pharmaceutical partners to fully unlock the potential of their molecules and provide better treatments for patients," said Barry Littlejohns, president of Catalent's Drug Delivery Solutions business. He added, "Combined with Catalent's existing technologies and network, the addition of Pharmatek's well-established scientific expertise and spray dry capabilities will create an unparalleled drug development platform, while the San Diego facility will expand our West Coast presence and provide additional access to the Asia-Pacific markets."

Pharmatek's site in San Diego is a cGMP facility that employs nearly 200 people, whose experience and expertise will complement Catalent's existing development and analytical services teams, based at multiple locations globally. Pharmatek provides development and analytical services for more than 120 molecules annually, and its facility comprises 68,000 square feet of laboratory, manufacturing and support space, with 2 analytical labs, 2 formulation labs, 4 engineering rooms, and 9 Certified ISO Class 8 manufacturing suites. The site also features 18,000 square feet of laboratory, manufacturing, and support space dedicated to development and manufacturing of highly potent compounds.

The transaction is subject to customary closing conditions and is expected to close in the next few weeks. Catalent intends to pay for this all-cash acquisition through a combination of existing cash and borrowings under Catalent's existing revolving credit facility. The acquisition will not change Catalent's fiscal 2017 financial guidance. The purchase price will not be disclosed as it is not material to Catalent's financial results.

Catalent is the leading global provider of advanced delivery technologies and development solutions for drugs, biologics, and consumer health products. With over 80 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance and ensuring reliable clinical and commercial product supply. Catalent employs approximately 9,200 people, including over 1,400 scientists, at 33 facilities across 5 continents, and in fiscal 2016 generated \$1.85 billion in annual revenue. Catalent is headquartered in Somerset, New Jersey. For more information, visit www.catalent.com.