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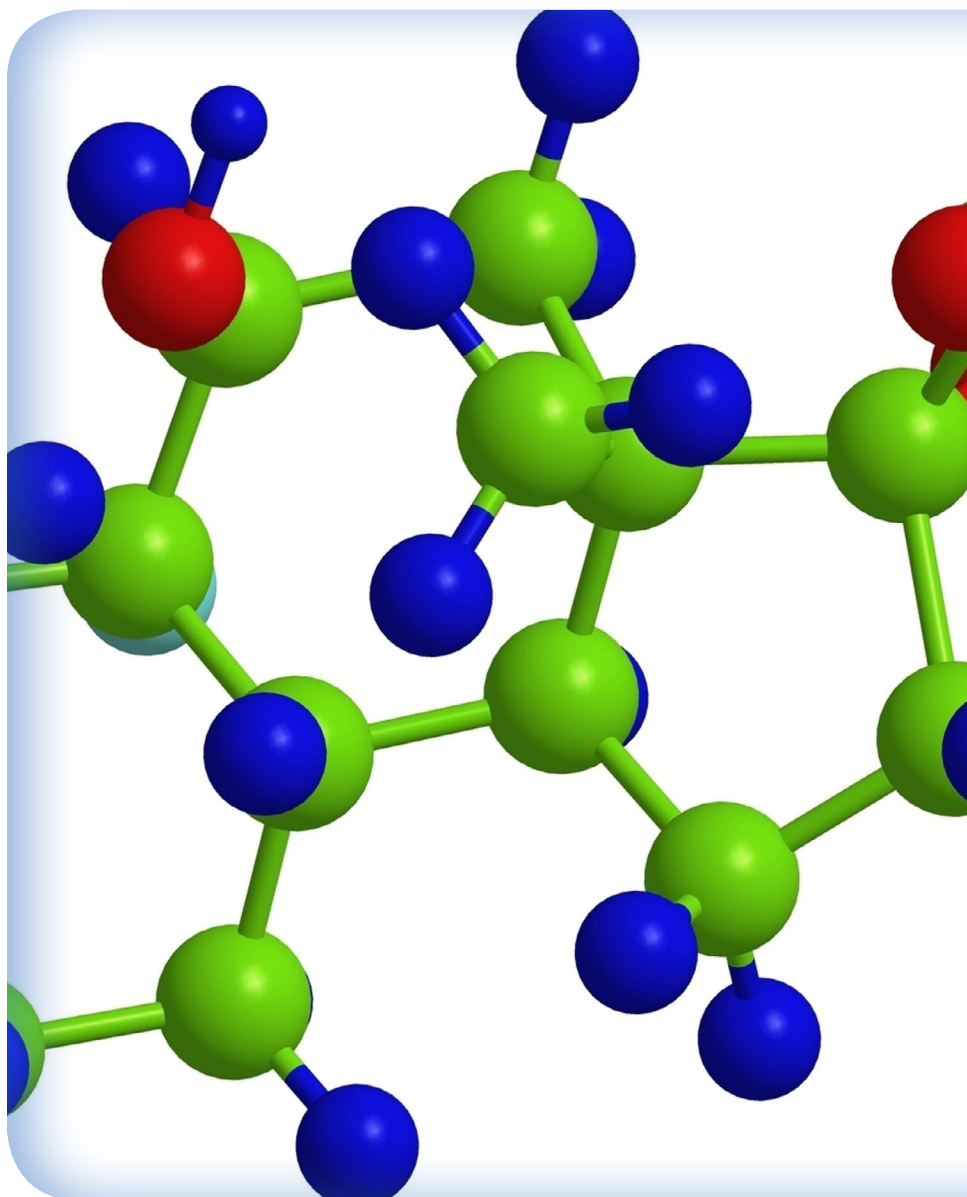
Formulation of Monodisperse  
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by Microfluidic Mixing Compared to  
Other Formulation Methods

Electrospun Nanofibers  
for Localized Delivery of  
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Parameters

Controlled Release of Sex  
Pheromone from Ester Wax/  
Polymer Bag Dispenser for  
Prevention of *Grapholita molesta*

Interview with Arto Urtti

Chapter News





**Kenneth Carson**  
*Editor*



**Ryan Donnelly**  
*Editor*



**Steven Giannos**  
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**Medha Joshi**  
*Editor*



**Arlene McDowell**  
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**Bozena Michniak-Kohn**  
*Editor*



**Rod Walker**  
*Editor*

# CRS Newsletter

Leading  
Delivery Science  
and Technology

Vol. 34 • No. 4 • 2017

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The *CRS Newsletter* is the official newsletter of the Controlled Release Society. The newsletter is published six times annually, providing scientific and technical information pertinent to the controlled release community and news about society and chapter activities. The newsletter is published online at [controlledreleasesociety.org](http://controlledreleasesociety.org).

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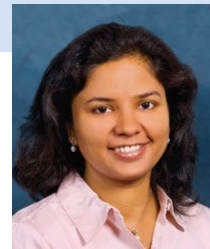
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*Medha Joshi  
Midwestern University, Chicago College of Pharmacy  
Downers Grove, IL, U.S.A.*

## Boston: City of Champions

The 44th CRS annual meeting was held in Boston, Massachusetts, the "City of Champions." Like the five-time Super Bowl champions, the New England Patriots, Boston has always been a champion of pharmaceutical innovation. In fact, Bloomberg Business ranked Massachusetts the #1 state for innovation with a total score of 93.33 on the Bloomberg State Innovation Index in 2016. It is home to two of the world's most prestigious universities—Harvard and MIT—and the CRS annual meeting lived up to these high standards with its focus on new developments in drug delivery science and innovation. CRS Boston had a total of 1,180 attendees from 42 countries.

I arrived a day early in Boston to participate in the wonderful MIT and Harvard field trip arranged by CRS. I enjoyed the day out in the sun, learning about the history of these prominent universities, the MIT Museum, and the John F. Kennedy Presidential Library. Hearing about the achievements of the universities, seeing the excellence in innovation in the MIT Museum, and learning about the tenure of President John F. Kennedy were motivating. It was a day very well spent.

My motivation elevated after listening to the much-anticipated opening plenary session by none other than the "Edison of medicine," Bob Langer of MIT. It was an excellent presentation packed with exciting stories of his research journey from a naïve researcher to an Institute Professor. Later, in a networking session for women in science, the inspiring speech by Paula Hammond (MIT) increased my passion for science. Paula's experiences resonated with many of the audience members, and they felt encouraged to do more.

The plenaries, pre-meeting workshops, and scientific sessions were a par excellence display of science. I am sure all those who attended the annual meeting personally would agree that the program had something for everyone. The program was a good mixture of researchers from universities, the pharmaceutical industry, clinical practice, and regulatory agencies.

In this fantastic issue of the *CRS Newsletter* you will find three Scientifically Speaking articles along with brief recaps of two chapter event. The interview with Arto Urtti is very energizing to all scientists in the drug delivery field. We also have the People/Companies in the News sections and a *DDTR* Update. ■



Tamara Minko, Ph.D.  
Rutgers, the State University of New Jersey, U.S.A.  
CRS President, 2017–2018

Dear current and future members of the Controlled Release Society,

It is with great pleasure I am writing to you as the new President of CRS. Thanks to those of you who believed I would be a good president and elected me to office. This is a tremendous honor for me and a huge responsibility.

For those who do not know me, I am a distinguished professor and chair of the Department of Pharmaceutics at Rutgers, the State University of New Jersey, U.S.A. My current research interests include drug and nucleic acids delivery, nanotechnology, personalized nanomedicine, biopharmaceutics, imaging, and molecular targeting. I am an executive editor for *Advanced Drug Delivery Reviews*, editor of *Pharmaceutical Research*, and a fellow of CRS, AAPS, and the American Institute for Medical and Biological Engineering (AIMBE). I'm a member several journal editorial boards, including CRS journals *Journal of Controlled Release* and *Drug Delivery and Translational Research*. And, it is hard to believe, but now I am a president of CRS—president #40. CRS was founded in 1978, so next year in the Annual Meeting in New York we will celebrate the 40th year of the society.

CRS is, in my opinion, one of the most respected and unique societies that covers new technologies and science in the multi-disciplinary delivery fields. CRS has succeeded in stimulating substantial progress in the areas of bioengineering, drug delivery, material science, pharmaceutics, consumer and diversified products, and veterinary science. With members in more than 30 countries, powerful local chapters all over the world, our excellent annual meetings, and two prestigious CRS journals, the *Journal of Controlled Release* (impact factor in 2016 of 7.786, editor-in-chief Kinam Park) and the recently established journal *Drug Delivery and Translational Research* (impact factor in 2016 of 3.094, editor-in-chief Vinod Labhasetwar), we can look into the future with deserved optimism.

I became a member of CRS 19 years ago in 1998 at the annual meeting in Los Angeles. At that time I was a postdoc in the laboratory of Henry Kopecek. My abstract was selected for an oral presentation. The next year, in 1999 at the annual meeting in Boston, my abstract again was selected for oral presentation, and together with Dr. Kopecek and co-authors, we received the Jorge Heller *Journal of Controlled Release* Outstanding Paper Award. I was extremely proud, and since that time, I have considered CRS as my primary and most important society. I decided to do my best for the success of CRS. In doing so, I was chair of the Annual Meeting Program Committee in 2008–2009 and a member of the CRS Board of Directors; I was inducted into the CRS College of Fellows and have received the *Drug Delivery and Translational Research* Journal Outstanding Paper Award. Also, graduate students and researchers from my lab three times received the Controlled Release Society Outstanding Pharmaceutical Paper Award.

Again, I'd like to stress that I am taking my role as CRS President very seriously and will do my best to keep the high prestige of the society.

Fortunately, I will not work alone. We have outstanding members on the CRS Board, and I'd like to recognize my colleagues who will share with me the leadership in CRS in 2017–2018. First of all, I'd like to express my sincere thanks to Immediate Past President Ruth Schmid (SINTEF Materials and Chemistry, Norway) for her tremendous efforts. She has led CRS with great dedication and passion during the past year and has made a lasting impact on our society through her leadership and through the implementation of changes to our annual meeting programming, increased industry focus, and the re-tooling of our strategic plan. I am very happy to work with the following CRS Board members: President-Elect Maria José Alonso (University of Santiago de Compostela, Spain), who successfully served on the Board in 2016–2017 as Secretary; current Secretary James Oxley (Southwest Research Institute, U.S.A.); Treasurer Jules Remenar (Dulce D Leche, U.S.A.); Treasurer-Elect Samir Mitragotri (Wyss Institute, Harvard University, U.S.A.); and five Directors-at-Large: Justin Hanes (John Hopkins University, U.S.A.), Richard W. Korsmeyer (retired from Pfizer, U.S.A.), Mark Prausnitz (Georgia Institute of Technology, U.S.A.), Nicole Papen-Botterhuis (Maxima Medical Centre, the Netherlands), and Ilva Rupenthal (University of Auckland, New Zealand).

I am very glad to report that Hamid Ghandehari (University of Utah, U.S.A.) agreed to serve as a chair of 2018 Annual Meeting Program Committee. We can be certain that with this committee led by Dr. Ghandehari we will have an outstanding meeting next year in New York. Our confidence for the further success of CRS is also based on the permanent help of the CRS committees, task forces, and our loyal team of volunteers, including the College of Fellows and past presidents of the society. I am asking for input and help from all of you. Please don't hesitate to reach out and contact me. I can be reached at [minko@pharmacy.rutgers.edu](mailto:minko@pharmacy.rutgers.edu). I look forward to your critiques, advice, and ideas.

I look forward to seeing you next year in New York at the 2018 CRS Annual Meeting! ■



## Congratulations to the 2017 Award Winners

CRS is honored to continue the tradition of recognizing the excellence of our members. You can find full biographies of awardees on the CRS website.

### Distinguished Service Award

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



Nicholas Peppas  
University of Texas at Austin, U.S.A.

### College of Fellows

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



Hongming Chen  
Kala Pharmaceuticals, Inc., U.S.A.



Sevdal Şenel  
Hacettepe University, Turkey



Patrick Sinko  
Rutgers University, U.S.A.



Kathryn Uhrich  
Rutgers University, U.S.A.



Ernst Wagner  
Ludwig Maximilians  
University, Germany

### Founders Award

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



Mark Saltzman  
Yale University, U.S.A.

### CRS T. Nagai Postdoctoral Research Achievement Award

*Cosponsored by The Nagai Foundation Tokyo*

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



Maike Windbergs  
Helmholtz-Institute for  
Pharmaceutical Research  
Saarland, Germany



Claus-Michael Lehr  
Helmholtz-Institute for  
Pharmaceutical Research  
Saarland, Germany

### Young Investigator Award

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



Zhen Gu  
University of North Carolina, U.S.A.

*continued*

## Drug Delivery and Translational Research Outstanding Paper Award

Cosponsored by Springer

*This award recognizes outstanding research in the field of drug delivery and translational research that was published during 2016 in Drug Delivery and Translational Research.*



Nathaniel Hwang  
Seoul National University, South Korea

Co-authors: Jiseung Heo, Rachel Koh, Whuisu Shim, Hwan Kim, Hyun-Gu Kim.

*Riboflavin-induced photo-crosslinking of collagen hydrogel and its application in meniscus tissue engineering. Drug Delivery and Translational Research: Volume 6, Issue 2, pages 148–158 (2016)*

## Jorge Heller Journal of Controlled Release Outstanding Paper Award

Cosponsored by Elsevier

*This award recognizes an outstanding regular paper related to the science of controlled release (not an invited, review, or special meeting paper) that was published during 2016 in the Journal of Controlled Release.*



Jaya Arya  
Georgia Institute of Technology, U.S.A.

Co-authors: Kristopher Dewitt, Maya Scott Garrard, Yu-Wei Chiang, Mark Prausnitz

*Rabies vaccination in dogs using a dissolving microneedle patch. Journal of Controlled Release: Volume 239, pages 19–26 (2016)*

## Graduate Research Advances in Delivery Science (GRADS) Award

Sponsored by Merck

*The Merck GRADS Awards are presented to graduate students who are presenting exceptional science in drug delivery at the CRS annual meeting. Award recipients were selected from the top-scoring abstracts that were submitted as poster presenters for the 2017 program, and final selection was reviewed by the CRS Annual Meeting Program Committee.*



Haiou Qu (poster 103): *Determination of globule size distribution of cyclosporine ophthalmic emulsion using asymmetric flow field flow fractionation*



Laura Gallagher (poster 171): *Development of functionalized hydrogels to enhance stem cell therapy for cardiac regeneration*



Monica B. Perez-Cuevas (poster 425): *Hepatitis B vaccination using a dissolvable microneedle patch*



Elana Ben-Akiva (poster 622): *Biomimetic anisotropic particles with naturally derived cell membranes*



Michael Mitchell (poster 624): *In vivo nanoparticle-mediated RNAi in the bone marrow niche enhances hematopoietic stem cell release*



Kelly Ibsen (poster 626): *Transdermal insulin delivery via a choline-based deep eutectic solvent*

continued

## 2017 Robert Langer Student Travel Grants

Congratulations to the following students who received the CRS Foundation Robert Langer Student Travel Grant to attend the 2017 CRS Annual Meeting in Boston.

Inela Bajrovic, *University of Texas at Austin, U.S.A.*  
James Fisher, *University of Pittsburgh, U.S.A.*  
Shiyang Jia, *Monash University, Australia*  
Manju Kanamala, *University of Auckland, New Zealand*  
Graeme Prospero-Porta, *University of Calgary, Canada*  
Emily Ryan, *Royal College of Surgeons in Ireland, Ireland*  
Phepafatso Tsae, *Carleton University, Canada*

## Local Chapter Young Scientist Travel Grants

*These travel grants aim to promote connectivity between various active CRS Local Chapters by providing travel grants to promising young scientists around the world to attend the CRS Annual Meetings.*

Congratulations to the 2017 CRS Local Chapter Young Scientist Travel Grant recipients! The following students received a travel grant to attend the 2017 CRS Annual Meeting in Boston.

### Canada Local Chapter:

Michael Dunne, *University of Toronto*  
Roy van der Meel, *University of British Columbia*

### Italy Local Chapter:

Enrica Chiesa, *University of Pavia*  
Antonella Grigoletto, *University of Padova*

### New Zealand Local Chapter:

Emma Kang, *University of Auckland*  
Hannah Vu, *University of Otago*

### Spanish-Portuguese Local Chapter:

Ana Cordeiro, *University of Santiago de Compostela*  
Ainhoa Gonzalez-Pujana, *University of Basque Country*

## 2018 Kinam Park Student Travel Grant Program

*The CRS Foundation Student Travel Grants are named in honor of CRS leaders who have made exceptional lifetime contributions to delivery science. CRS is honoring Kinam Park via funding student travel awards so promising young scientists can attend the CRS Annual Meeting in New York City, New York, U.S.A.*

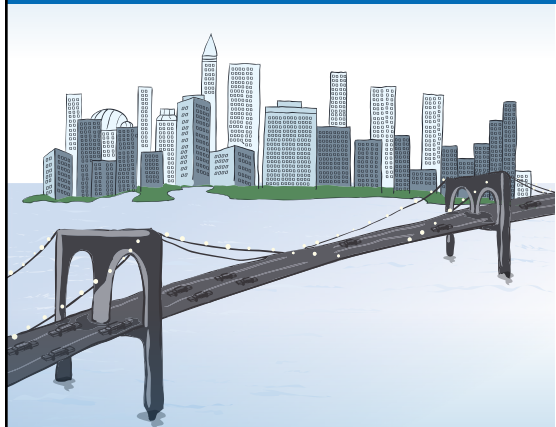


Kinam Park received his Ph.D. in pharmaceuticals from the University of Wisconsin in 1983. After postdoctoral training in the Department of Chemical Engineering at the same university, he joined the faculty of Purdue University in 1986. Since 1998, he has held a joint appointment in the Department of Biomedical Engineering, and he became the Showalter Distinguished Professor of Biomedical Engineering in 2006.

He has trained more than 60 Ph.D. graduate students and postdoctoral fellows. His research has been focused on the use of various polymers and hydrogels for controlled drug delivery. He is the founder and president of Akina, Inc., specializing in polymers for drug delivery. He is currently the editor-in-chief of the *Journal of Controlled Release*.

The Kinam Park Student Travel Grants are available only to current CRS student and postdoc members that have been accepted to present (either as an oral or poster) at the 2018 CRS Annual Meeting in New York. Award selection will be based on the quality of the applicant's science reflected in their research abstract, impact statement, and curriculum vita. ■

## 2018 Student Travel Grant Program Honors Kinam Park



Future leaders need a strong foundation. Help CRS celebrate and honor Kinam Park while supporting its future leadership. Your donation will support travel grants for students to attend the 2018 CRS Annual Meeting in New York.



For more information and to donate visit  
[controlledreleasesociety.org/donate](http://controlledreleasesociety.org/donate)



# A Focus on Ocular Delivery: Interview with Arto Urtti

*Vishwas Rai<sup>1</sup> and Bozena B. Michniak-Kohn<sup>2</sup>*



*Arto Urtti*

Arto Urtti is a professor of biopharmaceutics at the University of Helsinki and University of Eastern Finland. At the University of Helsinki he has headed the Centre for Drug Research within the Faculty of Pharmacy. He has also been the editor-in-chief of the *European Journal of Pharmaceutical Sciences* (2001–2011) and academic editor of *PLoS ONE* (2007–2012), and he serves as a scientific advisor for several international pharmaceutical companies. He has been a part of CRS's governance in the past. His main research field is drug delivery, primarily ocular drug delivery. This involves technologies for controlled release, preclinical pharmacokinetics and modeling, and pharmaceutical nanotechnology (biomaterials for drug and gene targeting and for three-dimensional cell cultures).

Dr. Urtti received his Ph.D. degree in 1986 from the University of Kuopio, Finland. He obtained international research experience as a postdoctoral fellow in the Department of Pharmaceutical Chemistry, University of Kansas, and was a visiting professor at both the Department of Bio-Pharmaceutical Sciences, University of California, San Francisco (UCSF) and the Department of Pharmaceutics, University of Wisconsin. He has published over 300 peer-reviewed articles as well as 24 patents and patent applications.

He has evaluated grant applications for the scientific funding bodies from more than 10 countries including the European Union (EU-FP7, ERC), Medical Research Council (U.K.), Wellcome Trust, and French National Research Agency.

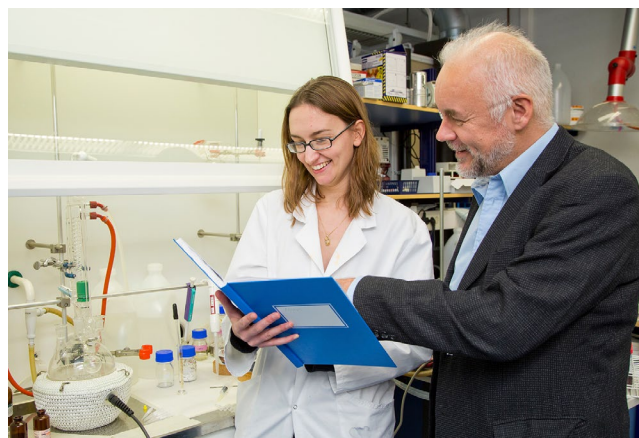
His research has been funded by the Academy of Finland, European Union, U.S. Food and Drug Administration (FDA), and the pharmaceutical industry. For his research contributions, Dr. Urtti has received numerous scientific awards including the American Association of Pharmaceutical Scientists Fellowship, honorary membership in the Finnish Pharmacists' Association, invited membership in the Finnish Academy of Science and Letters, City of Kuopio Golden Recognition Medal, Albert Wuokko Prize, Millennium Distinction Award, European Federation for Pharmaceutical Sciences (EUFEPS) Distinguished Service Award, and EUFEPS Senate membership.

**Q** *You have achieved great success in your career. Please mention some of your mentors and the experiences you have shared with them.*

**A** Lotta Salminen, professor of ophthalmology, was my mentor during my Ph.D. studies. We investigated ocular pharmacokinetics and showed the role of pigment binding of pilocarpine and timolol in the eye as well as the surprisingly fast systemic absorption of ocular drugs. She introduced me to the international community of ocular drug research. Later, Frank Szoka was my mentor during my sabbatical at UCSF School of Pharmacy. During that period I learned a lot from him about nonviral gene delivery and nanomedicine in general. The research project was about DNA transfer to the retinal pigment epithelium. Frank's research is very impressive: cutting edge, innovative, mechanistic, well-controlled, and free of hype. Excellent scientific role model.

**Q** *You have spent your time in both the United States and Europe. How would you describe your personal and professional life challenges during the intercontinental portion of your career? What advice will you offer current professionals for their scientific journeys?*

**A** Research periods in the United States were great both scientifically and personally. Certainly, I recommend international postdoctoral and sabbatical research periods. Of course, there are challenges, such as moving with a family, school arrangements for the kids, and work career aspects for the spouse. For me and my family, the experiences were valuable and certainly worth the efforts. For example, the kids got experience that built their self-confidence in international environments. In the international research environment one becomes exposed to many cultures, people, research environments, and scientific discussions. International experience is an intellectual investment, and the research data generated during that period are only a small part of the whole thing. The international research period



*In the lab with French postdoc Emmanuelle Morin-Picardat.*

*continued*

<sup>1</sup>Independent consultant, 39206 Guardino Drive, Fremont, CA, U.S.A.

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



stimulates thinking, improving the understanding of science and perhaps other aspects of the world as well. Currently, the European Union is heavily supporting scientific mobility between EU countries. This is a fantastic development providing nice opportunities also for pharmaceutical scientists.

**Q** *In today's world, how important is it for an academician to be connected to industry? How did you get your first industrial collaboration?*

**A** Well, this depends very much on the field, but in the field of drug delivery it is important. Industrial collaborations help to understand the needs in industrial research and development, and they introduce the Ph.D. students and postdocs to industrial issues and personnel. This kind of mobility is nicely built into the Marie Curie programs in the EU, where Ph.D. students have training periods in companies. My first industrial grant was from Merck (U.S.A.), since my postdoctoral period in Kansas was partly supported by Merck. In fact, Merck granted me three-year funding in Finland to continue the project on ocular drug delivery after my postdoc period in the United States. Since then I have had many industrial collaborations with companies from Finland and other European countries, Japan, and the United States.



*In the campus at University of Eastern Finland.*

**Q** *Please share details on some of the important projects at the Centre for Drug Research. What is its vision? Is it under an academic umbrella?*

**A** The Centre for Drug Research in Helsinki is an academic umbrella organization, not a department in the administrative sense. It aims to develop new approaches for drug discovery and research. We have some exciting research related to drug delivery involving several research groups. For example, Vincenzo Cerullo's team is doing cutting-edge work on cancer immunotherapy that is based on coating of adenoviruses with specific peptide mixtures. Marjo Yliperttula's group is advancing nicely in the research on extracellular vesicle structure and function. This work leads to new insights in the design of targeted drug carriers. Alex Bunker is a computational physicist who has specialized in the molecular dynamics of liposomes. This work nicely complements the experimental research in the Centre. Finally, I would like to mention EU OpenScreen, the European international infrastructure for chemical biology and drug discovery where the Centre is one of the nodes. This is a new initiative that starts this year. It will provide biologists an avenue to screen large sets of chemicals against their biological targets, and for chemists it offers opportunities to include their compounds in the collections of EU OpenScreen for further biological testing. Perhaps, the field of drug delivery and targeting will also benefit from this screening activity.

**Q** *Please share some of the important research publications coming out of your research lab. Outline the significance and contributions made to pharmaceutical sciences.*

**A** Here are four important articles.

Bhattacharya, M, Sarkhel, S, Peltoniemi, J, Broadbridge, R, Tuomainen, M, Auriola, S, Urtti, A. Differentially cleaving peptides as a strategy for controlled drug release in human retinal pigment epithelial cells. *J. Controlled Release* 251: 37-48 (2017). This was the cover story in *JCR* recently with a preface from Kinam Park. The study introduces peptide sequences that can be used to control cargo compound release rate from the conjugate within the retinal pigment epithelial cells. The functionality of the concept was shown quantitatively with LC/MS analytics. This technology opens new possibilities for retinal drug delivery.

Lajunen, T, Kontturi, LS, Viitala, L, Manna, M, Cramariuc, O, Róg, T, Bunker, A, Laaksonen, T, Viitala, T, Murtomäki, L, Urtti, A. Indocyanine green loaded liposomes for light triggered drug release. *Mol. Pharm.* 13: 2095-2107 (2016). Indocyanine green is an FDA-approved clinical imaging dye. The compound was used to induce near-IR light triggered drug release from liposomes. This feature may be useful in site- and time-controlled drug delivery.

Vellonen, KS, Soini, EM, Del Amo, EM, Urtti, A. Prediction of ocular drug distribution from systemic blood circulation. *Mol. Pharm.* 13: 2906-2911 (2016). This is the first publication that illustrates the pharmacokinetic principles and model for drug distribution from the blood stream to the posterior eye segment. Understanding ocular distribution is important in drug design in two ways: 1) targeting drugs to the eye from systemic circulation on purpose and 2) avoiding ocular exposure and potential retinal toxicity of drugs that are intended for other targets.

Del Amo, EM, Rimpelä, AK, Heikkinen, E, Kari, OK, Ramsay, E, Lajunen, T, Schmitt, M, Pelkonen, L, Bhattacharya, M, Richardson, D, Subrizi, A, Turunen, T, Reinisalo, M, Itkonen, J, Toropainen, E, Casteleijn, M, Kidron, H, Antopolsky, M, Vellonen, KS, Ruponen, M, Urtti, A. Pharmacokinetic aspects of retinal drug delivery. *Prog. Retin. Eye Res.* 57: 134-185 (2017).

Comprehensive and analytical review of pharmacokinetics related to retinal drug delivery. Literature was critically reviewed and supplemented with new analyses of literature data and kinetic simulations to provide new insights. I think that this is good reading material for academic and industrial researchers who want to learn about retinal drug delivery.

**Q** You have been an editor of multiple international journals. Please share some of your insights on where drug science and publishing are progressing.

**A** One strong trend in drug science (and many other fields) is related to the improved efficacy of data use. Open public data sources will be launched, and this will give better chances to further analyze and model the data. Also, the various analytical tools are getting better at helping to generate new data at high sensitivity and resolution. I am sure that these trends will foster scientific progress.

However, I am also worried about the publishing activities. There are numerous new journals popping up, and they are not maintaining good scientific standards. Another worrying trend is the “marketing” of research results by the research groups. I am in favor of the classic scientific idea of truth searching. Unfortunately, we see plenty of hype and marketing of drug delivery technologies even in good journals. I wonder about the reproducibility of all that research. This is wide problem, not only in the field of drug delivery.

**Q** Please mention research publications (other than your own) that you believe are key articles in the pharmaceutical field.

**A** Maurice, DM, Mishima, S. Ocular pharmacokinetics. In: Pharmacology of the Eye. ML Sears, ed. Springer-Verlag, Berlin, Germany, pp. 19-116 (1984). Excellent, profound, and comprehensive treatise on ocular pharmacokinetics. David Maurice was always ahead of his time.

Amidon, GL, Lennernäs, H, Shah, VP, Crison, JR. Theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res.* 12: 413-420 (1995). Starting point for biowaivers. Nice analysis of the roles of dissolution and permeability factors in drug absorption.

Hidalgo, IJ, Raub, TJ, Borchardt, RT. Characterization of the human colon carcinoma cell line (Caco-2) as a model system for intestinal epithelial permeability. *Gastroenterology* 96: 736-749 (1989). Introduction of the Caco-2 model to pharmaceutical research. This study had a big impact on the ways that drug delivery issues are investigated.

Fox, ME, Szoka, FC, Frechet, JMJ. Soluble polymer carriers for the treatment of cancer: The importance of molecular architecture. *Acc. Chem. Res.* 42: 1141-1151 (2009). Nice study that shows the fundamental importance of polymer shape on its plasma clearance.

Ghetie, V, Popov, S, Borvak, J, Radu, C, Matesoi, D, Medesan, C, Ober, RJ, Ward, ES. Increasing the serum persistence of an IgG fragment by random mutagenesis. *Nat. Biotechnol.* 14: 637-640 (1997). Demonstrates the mechanism for the long persistence of IgG compounds in the plasma. Such antibodies became highly successful drugs in many indications.

**Q** What closing thoughts would you like to share?

**A** Drug delivery is an exciting field with ever-increasing importance. I have enjoyed working in this field, since it integrates nicely together chemistry, mathematic modeling, pharmaceutical sciences, and medicine. The multidisciplinary nature of the field makes it also fruitful for academic, industrial, and regulatory collaborations—great learning experiences. Certainly, I can recommend this field to young scientists, but it is important to find new approaches and niche areas that are not fully occupied already. ■



In the office at University of Helsinki.

# Formulation of Monodisperse Non-Ionic Surfactant Vesicles (NISV) by Microfluidic Mixing Compared to Other Formulation Methods

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## Introduction

Non-ionic surfactant vesicles (NISV), or “niosomes,” are synthetic bilayer vesicles typically formed by the self-assembly of non-ionic surfactants, cholesterol, and the addition of a charged species. NISV exhibit more advantages over liposomes, in terms of cost and stability, and constituent surfactants have a wider range of chemistries that can be selected to provide greater potential for innovation related to vesicle composition. NISV have been used to deliver hydrophilic drugs that are encapsulated in the interior aqueous compartment or adsorbed on the bilayer surface, as well as hydrophobic drugs that are localised within the lipid bilayer of the NISV.<sup>1</sup> Various methods have been used in vesicle preparation, providing different characteristics. We have investigated the physical characteristics of NISV prepared by three different manufacturing methods: thin-film hydration (TFH), heating method, and microfluidic mixing. The main factors affecting the control of NISV production by microfluidics were also given careful consideration.

## Experimental Methods

NISV formulations composed of monopalmitin glycerol (MPG), cholesterol (Chol), and dicetyl phosphate (DCP) in a molar ratio of 5:4:1 of MPG/Chol/DCP were prepared by the three methods as previously described.<sup>2</sup> NISV suspensions prepared by the TFH and heating methods were manually extruded using an Avanti miniextruder containing a 100 nm pore diameter polycarbonate membrane at 50°C to reduce the particle size and distribution. Physical characteristics such as particle size, polydispersity index (PDI), and zeta potential (ZP) were measured by dynamic light scattering. Morphological examination of the NISV was performed by atomic force microscopy (AFM).

## Results and Discussion

Dynamic light scattering revealed that the particle size of the extruded NISV prepared by the TFH method and heating method were small and monodisperse, whereas the non-extruded particles were large and polydisperse (Table 1). However, particles prepared by microfluidic mixing were small with a narrow particle distribution. Moreover, because all the particles prepared by the three methods used the same lipid compositions, the ZP values for the extruded particles prepared by the TFH and the heating methods and by microfluidics were the same with no significant difference ( $P > 0.05$ ) (Table 1). Microfluidics produces small, monodisperse particles in minutes, whereas the other methods took hours to obtain equivalent results. Traditionally, the production of small particles using the TFH and heating methods requires the use of a post-manufacturing size-reduction step to produce particles of the required size and to reduce the PDI. This has restricted the use of these methods to bench scale because a much longer industrial-scale process is required to produce a consistently sized end product. However, microfluidic mixing allows larger scale production of controlled particle sizes with homogenous distribution in a single step without the need for post-manufacturing size reduction.

Regarding the stability of the NISV, the TFH and heating methods (post extrusion) and microfluidic mixing produced stable particles with respect to size with no significant change when stored at four different temperatures over two months (Fig. 1). This suggests that

**Table 1. Comparison of Particle Characteristics Prepared by the TFH Method, Heating Method, and Microfluidic Mixing ( $n = 3$ ,  $\pm$ SD)<sup>a</sup>**

Method of Preparation	Size (nm)	PDI	ZP (mV)
TFH (before extrusion)	1,027.17 $\pm$ 75.79	0.83 $\pm$ 0.03	12.30 $\pm$ 3.22
TFH (after extrusion)	124.70 $\pm$ 0.72	0.12 $\pm$ 0.01	-28.70 $\pm$ 1.39
Heating method (before extrusion)	3,938.00 $\pm$ 95.25	0.85 $\pm$ 0.04	-14.50 $\pm$ 1.25
Heating method (after extrusion)	152.34 $\pm$ 1.76	0.10 $\pm$ 0.02	-36.67 $\pm$ 3.14
Microfluidic mixing	165.90 $\pm$ 0.92	0.08 $\pm$ 0.02	-31.38 $\pm$ 1.80

<sup>a</sup>TFH = thin-film hydration; PDI = polydispersity index; and ZP = zeta potential. Reproduced by permission from Elsevier.<sup>2</sup>

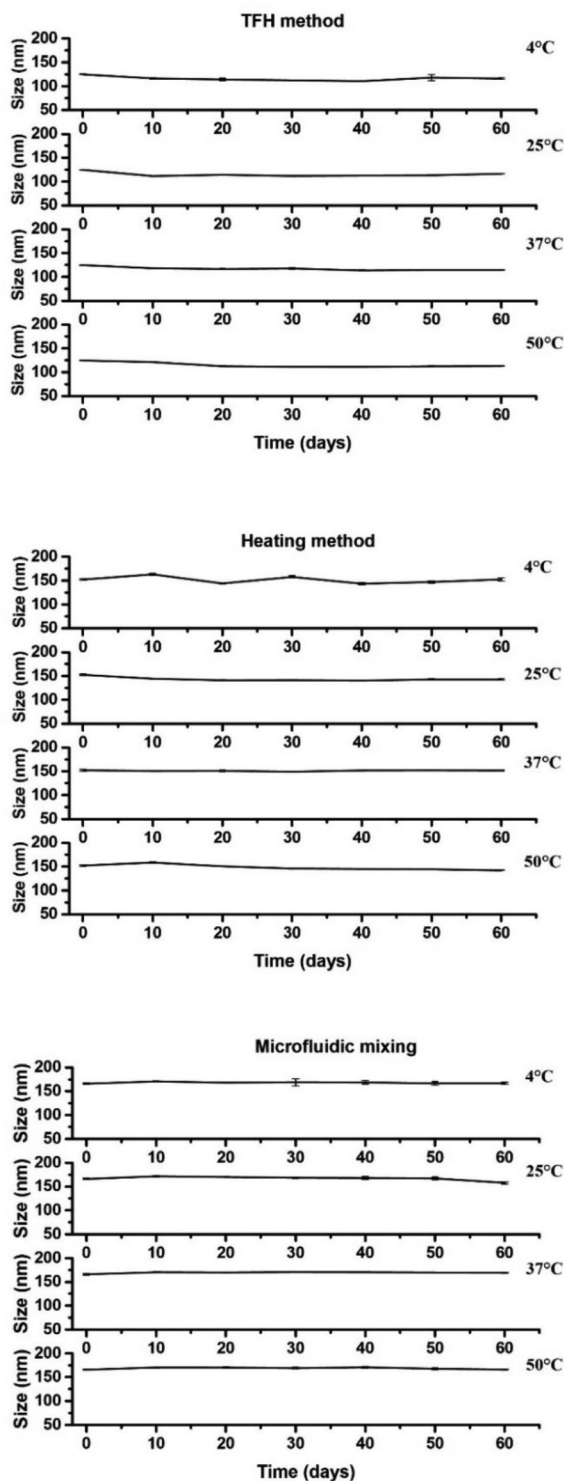
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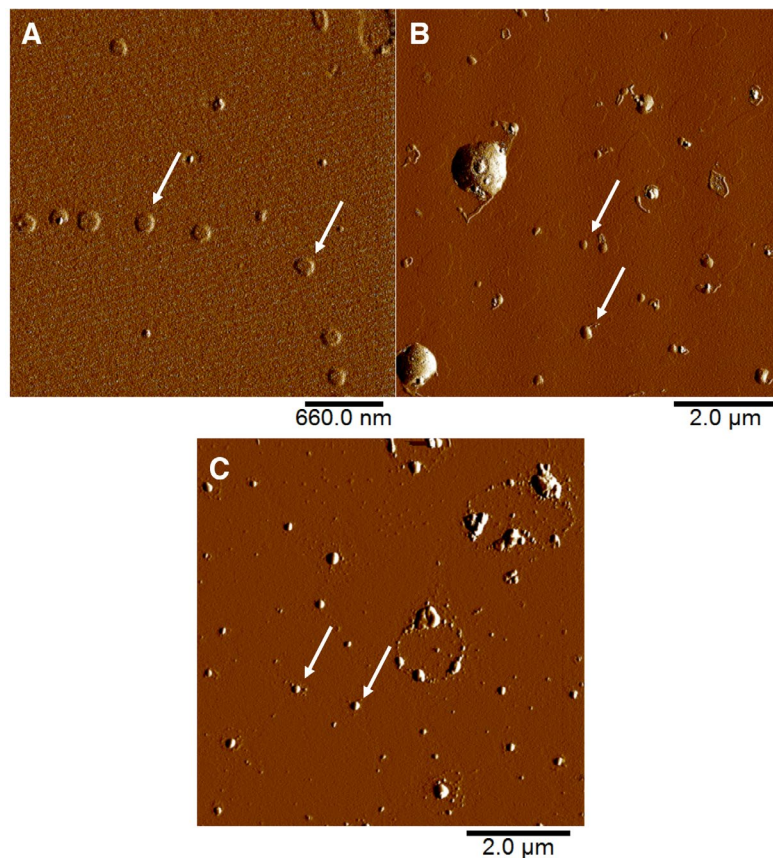


**Figure 1.** Size stability of NISV prepared by the thin-film hydration (TFH) method, heating method, and microfluidic mixing and stored over 60 days at 4, 25, 37, and 50°C. The data represent the mean  $\pm$  SD ( $n = 3$ ). © Elsevier, reproduced by permission.<sup>2</sup>

the method of preparation had no effects on particle stability. Although temperature can have an energy input into the system and can sometimes lead to changes in the crystalline structure of the lipids and potentially cause changes in the ZP that might affect the stability of the particles,<sup>3</sup> in this study all three methods exhibited excellent stability over the range of temperatures (4, 25, 37, and 50°C) with no significant increase in the average particle size, PDI, and ZP ( $P > 0.05$ ) when stored for two months even at the higher storage temperatures. These data indicate that microfluidics not only enables rapid, robust, and scalable production of NISV but also supports the stable formation of these vesicles, which is necessary for applications requiring prolonged shelf life such as pharmaceutical drug delivery.

Morphological observations of AFM images confirmed the formation of spherical particles of NISV regardless of the method of preparation (Fig. 2). These results confirmed that the particles prepared by microfluidics in a single step are similar to the extruded particles prepared by the more traditional TFH and heating methods.

For the formation of lipid-based particles through microfluidic mixing, the total flow rate (TFR) and the flow rate ratio (FRR) of aqueous to solvent

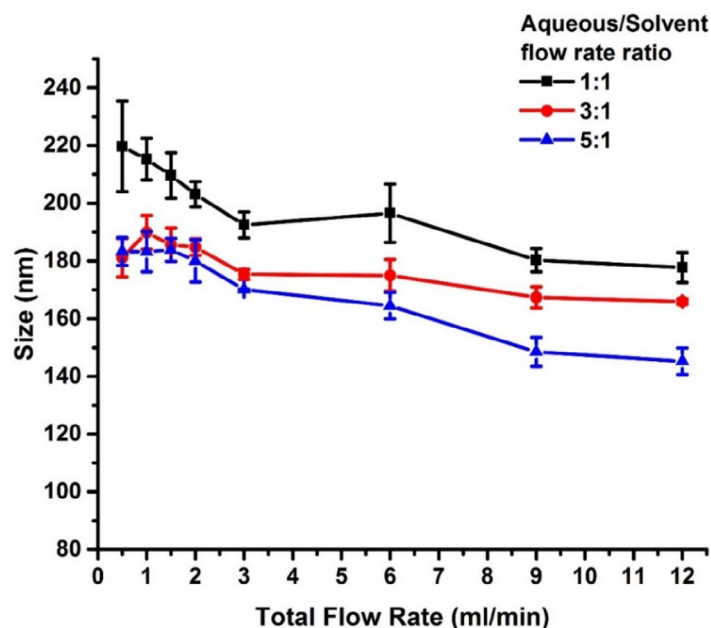


**Figure 2.** AFM images of NISV prepared three methods: (A) thin-film hydration method post extrusion, (B) heating method post extrusion, and (C) microfluidic mixing. © Elsevier, reproduced by permission.<sup>2</sup>



streams were anticipated to be crucial factors in particle preparation.<sup>4,5</sup> Figure 3 shows the changes of the particle size by changing the FRR from 1:1 to 5:1 (aqueous/lipid phases) and the TFR from 0.5 to 12 mL/min.

As the aqueous/ethanol FRR increased from 1:1 to 5:1, a significant ( $P < 0.05$ ) reduction in NISV size was observed and found to be TFR dependent. At a TFR  $< 3$  mL/min, the difference between the particle size prepared at FRR of 3:1 and 5:1 was not significant ( $P > 0.05$ ). However, at higher TFR ( $> 3$  mL/min), the difference between these two FRRs was significant ( $P < 0.05$ ). The FRR strongly affected the final solvent concentration. At lower FRR (1:1), the final solvent concentration increased, thus boosting the production of larger particles owing to particle fusion and lipid exchange, whereas at higher FRR (5:1), the chance of producing large particles was reduced as a result of decreased solvent concentration. Moreover, the TFR was shown to have a significant ( $P < 0.05$ ) effect on particle size, in which the increase in the TFR from 0.5 to 9 mL/min resulted in an overall reduction in particle size at all the FRR. However, further increase in the TFR above 9 mL/min was not associated with a significant decrease in particle size at all the FRR. The effect of the TFR on particle size is still debatable. Although some researchers have reported that TFR does not have a significant effect,<sup>6</sup> others have reported the contrary.<sup>7</sup> In our previous work, we have demonstrated that the aqueous medium used also has a significant effect on NISV characteristics when prepared by microfluidics.<sup>8</sup> So microfluidic mixing allows the production of NISV with a tuned particle size by varying the TFR, FRR, and aqueous medium.



**Figure 3.** Size changes of NISV prepared at different total flow rate and flow rate ratio of the aqueous and lipid phase. The data represent the mean  $\pm$  SD ( $n = 3$ ). © Elsevier, reproduced by permission.<sup>2</sup>

## Conclusions

In this work, the characteristics of NISV prepared by microfluidics were compared with those prepared by the conventional TFH and heating methods. Microfluidic mixing enabled preparation of small, monodisperse particles in a single step, without the need of a size-reduction step as in the case of the other methods. The method of preparation did not have significant effects on particle stability. Using microfluidic mixing, a homogenous NISV suspension was prepared with high reproducibility. FRR and TFR between the two phases of the microfluidic mixing are factors that have significant effects on particle characteristics, which can be optimised to produce NISV with a defined size, which is important in developing an effective drug delivery system. This work demonstrates the promise of microfluidic mixing in NISV preparation to facilitate the development and optimisation of these dispersions for nanomedicine applications at both bench and industrial scales.

## Acknowledgements

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# Electrospun Nanofibers for Localized Delivery of Dexamethasone: Preliminary Investigation on Formulation Parameters

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## Introduction

Electrospinning is an electrostatic fiber fabrication technique producing homogeneous fibers in the nanometer range. The process involves dropping a polymer solution in an electric field in such a way that the electric forces overcome the polymer solution surface tension and the drop is stretched, forming a stable Taylor cone and eventually depositing polymer fibers on a metal collector (Fig. 1B). The process can take place starting from a polymer solution or melted polymer. Using a polymer solution enables working at room temperature conditions, but it introduces a solvent whose evaporation should be completed before the fiber is removed from the collector, whereas using a melted polymer at high temperatures can be detrimental for the polymer and/or other nanofiber constituents. A lot of literature on the topic can be found, explaining the technique, the parameters and process conditions affecting fiber formation, its applications, and reporting polymers used in electrospinning.<sup>1</sup> Summarizing, it can be said that electrospinning is a simple one-step technique to produce nanofibrous matrices useful in different areas; however, its potentialities have not been completely developed yet, and the process should be studied according to the single polymer or combination of polymers to be processed. In the biomedical field, electrospun matrices made of biodegradable biocompatible polymers show interest as temporary scaffolds for tissue regeneration.<sup>2–5</sup> Recent studies have shown that nanoscale fibers presenting high area/volume ratio, high interconnectivity, and superior biomechanical properties could have advantages also as drug delivery systems, including high drug loading efficiency, drug controlled release, excellent stability, and/or improvement of bioactive molecules' apparent solubility. Moreover, the encapsulation of active molecules into electrospun nanofibers can be exploited to perform local delivery to a target site.<sup>5,6</sup>

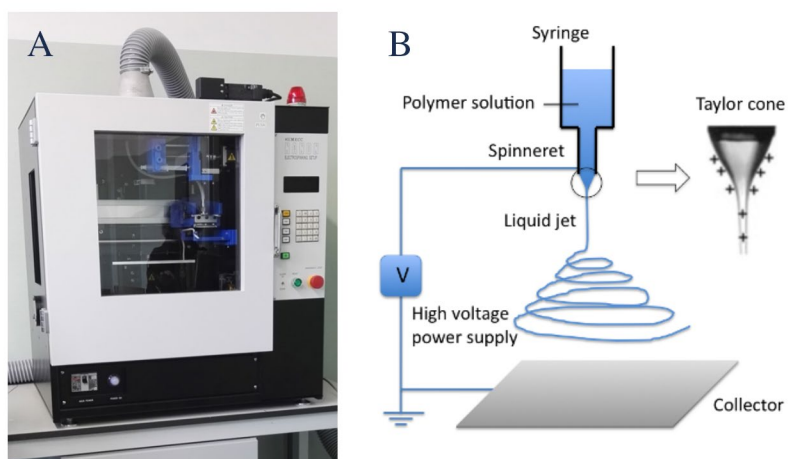
The preliminary study is focused on manufacturing, characterization, and *in vitro* evaluation of electrospun nanofiber matrices (EINanoMats) made of the biodegradable copolymer polylactide-*co*-poly- $\epsilon$ -caprolactone (PLA-PCL) and loaded with dexamethasone (DXM), whose application could be local delivery of DXM through patches for treating skin diseases (e.g., keloid and psoriasis).

## Experimental Methods

**Preparation of Electrospun Matrices.** PLA-PCL 70:30 (125,000 Da molecular weight, glass transition temperature 42°C, Evonik Nutrition & Care, Darmstadt, Germany) and DXM were processed through a NANON-01A electrospinning apparatus (MEEC Instruments, Pioltello, Italy) (Fig. 1A). Solvent, co-solvent selection, and polymer concentration were performed through a theoretical model based on the Mark-Houwink equation and Berry number followed by their experimental evaluation.<sup>1,7,8</sup>

PLA-PCL (10–25% w/v) and DXM (0.01% w/w) were solubilized in CH<sub>2</sub>Cl<sub>2</sub>/dimethylformamide mixture (70:30 ratio). The solution was pumped through a syringe at an 0.8 mL/h flow rate using 18 and 27 gauge needles and keeping the needle end and collector at a distance of 15 cm. Voltage was varied from 20 to 23 kV until a stable Taylor cone was reached; orientation of various fibers was obtained using different collectors, such as plate and rotating collectors.

**Characterization of Electrospun Matrices.** DXM-loaded EINanoMats were characterized for their morphology by scanning electron microscopy (SEM) with a Zeiss EVO MA10 apparatus (Carl Zeiss, Oberkochen, Germany) and for mechanical properties with an Enduratec ElectroForce 3200 apparatus. An *in vitro* dissolution test was performed in 0.1M HEPES



**Figure 1.** (A) NANON-01A electrospinning apparatus (MEEC). (B) Schematic showing electrospinning functioning mechanism.

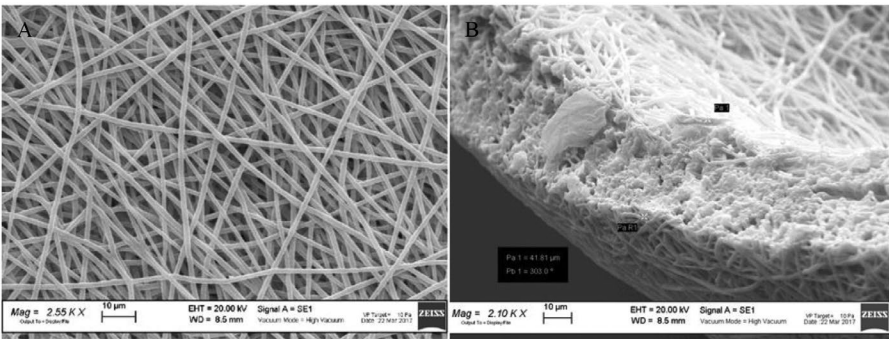
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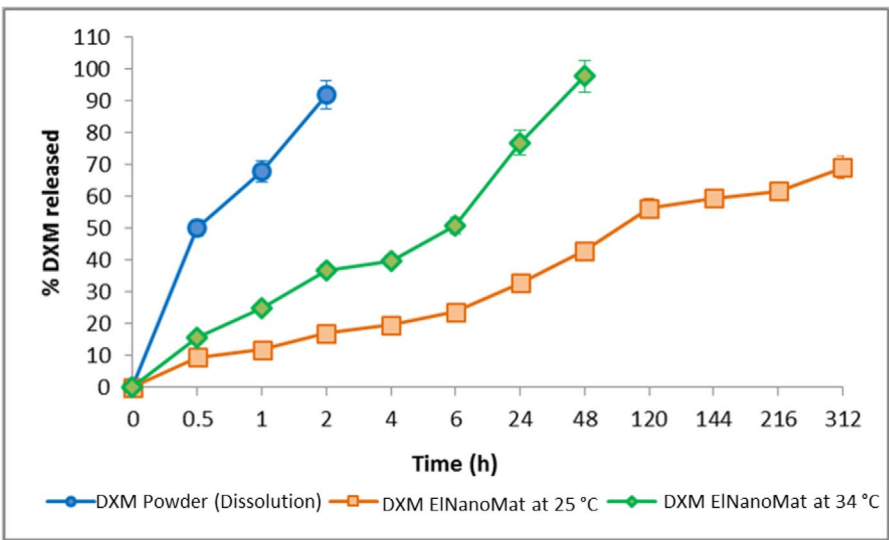
(pH 7.4) at 25 and 34°C. DXM content and release profile from electrospun nanofibers were evaluated by an Agilent HPLC (Agilent Italia, Cernusco sul Naviglio, Italy) equipped with a hydrophobic C18 Zorbax Eclipse Plus column, 4.6 × 15 cm, 5 µm; the mobile phase was Milli-Q water and acetonitrile 60:40 with a flow rate of 1 mL/min. Analyses were performed with an ultraviolet detector at 238 nm wavelength. The EInanoMat *in vitro* degradation test was performed by incubating DXM-loaded electrospun nanofibers in phosphate-buffered saline (0.05 mM, pH 7.4) at 34°C and evaluating the polymer weight average molecular weight (Mw), number average molecular weight (Mn), and polydispersity index (PI) with an Agilent Infinity series GPC system equipped with three Ultrastaygel columns connected in series (7.7 × 250 mm each with different diameter of the pores: 10<sup>4</sup>, 10<sup>3</sup>, and 500 Å) and an infrared detector.



**Figure 2.** SEM images of (A) DXM-loaded EInanoMat surface and (B) DXM-loaded EInanoMat section.

**Table 1. Results of Mechanical Tests on Placebo- and DXM-Loaded EInanoMats: Strain (ε), Stress (σ), Elastic Modulus (E), and Loading at Break (P)**

Mechanical Test Parameters	Placebo EInanoMats	DXM-Loaded EInanoMats
ε (mm/mm)	0.045 ± 0.004	0.050 ± 0.004
σ (MPa)	0.9 ± 0.06	0.9 ± 0.05
E (MPa)	35.481 ± 2	34.970 ± 1.8
P (N)	2.904 ± 0.3	2.858 ± 0.3



**Figure 3.** DXM release from EInanoMats at 34 and 25°C in 0.1M HEPES. Dissolution of DXM powder at 34°C in 0.1M HEPES was used as the control.

Results and Discussion

Morphology of EInanoMats shows that both polymer concentration and needle diameter highly affect the size and size distribution of nanofibers.<sup>7</sup>

Owing to their stability in spite of syringe needle gauge and their fiber regular shape, EInanoMats obtained from PLA-PCL 20% were chosen for DXM loading. The drug was homogeneously dispersed inside EInanoMats, and no evidence of drug crystals on nanofiber surfaces was detected by SEM (Fig. 2A). Thickness of DXM-loaded EInanoMats was 41.81 ± 9.6 µm, with a higher thickness in the central part of the matrices and the lowest at the borders. Nanofiber entanglement was homogeneous and created fiber porosity in its three-dimensional environment, as shown in the EInanoMats SEM section (Fig. 2B). Results of the *in vitro* degradation test showed that EInanoMats (placebo and DXM loaded) were stable for up to 21 days without any significant copolymer Mw, Mn, and PI change.

The values reported in Table 1 show that elastic modulus and loading at break values of EInanoMats are suitable for biomedical applications such as skin repairing and tissue regeneration (e.g., esophagus temporary substitution). DXM loading does not modify EInanoMats’ mechanical behaviour.

The results of the *in vitro* dissolution test reported in the graphs of Figure 3 show that EInanoMats are able to slow down DXM release up to 120 h. Drug release is highly affected by temperature, consistent with the PLA-PCL glass transition temperature.

Conclusions

Structural features of nanofibers and their good stability in physiological conditions make these EInanoMats an alternative drug delivery system for topical extended release of DXM (e.g., for application in skin disorders).

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# Controlled Release of Sex Pheromone from Ester Wax/Polymer Bag Dispenser for Prevention of *Grapholita molesta*

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## Introduction

*Grapholita molesta* insects (GM) inhabit fruit trees (e.g., peach, apple, and pear), and their larvae destroy fruit.<sup>1</sup> Although various pesticides have been used for prevention of GM, the larvae cannot be prevented from entering fruit.<sup>1</sup> Sex-pheromone-mediated mating disruption (MD) has been implemented to reduce the larval population by various types of MD dispensers.<sup>2</sup> The principle is that male insects follow ghost females with artificial pheromones released by an MD dispenser instead of actual female insects (Fig. 1).<sup>2</sup> Because male insects have only one chance to mate during their life, an MD dispenser can steal the one mating opportunity.<sup>2</sup>

GM is active from April to September, and they produce a new generation four or five times per year.<sup>2</sup> Therefore, a dispenser is required to release GM pheromone constantly for 6 months. Various types of MD dispensers have been commercialized such as reservoir, microemulsion, and wax.<sup>3</sup> However, the duration of pheromone release from the MD dispensers is short and is insufficient to cover all generations of GM insects, and the release rate varies with climate changes.<sup>3</sup>

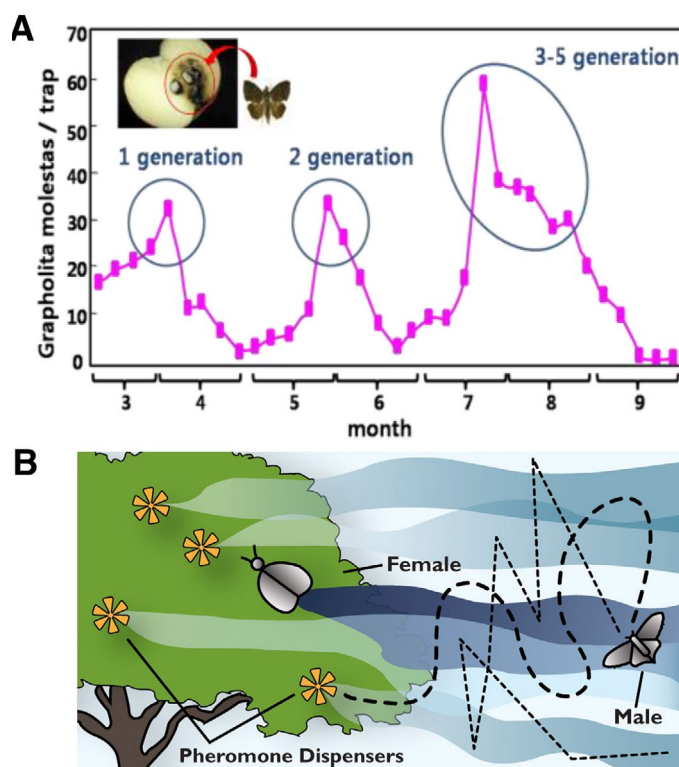
Paraffin wax and polyethylene polymer have been reported as the dispenser materials for sustained release of GM pheromone.<sup>4</sup> Generally, the release rate of the active ingredient can be controlled by the solubility with carrier materials or using a diffusion barrier.<sup>4</sup> Thus, ester waxes (beeswax, Japan wax, and carnauba wax) that have a similar chemical structure with GM pheromone were studied to prove that the solubility of GM pheromone affects the release pattern of GM pheromone. In this study, four kinds of waxes and polymer film bags were screened as dispenser materials compared with paraffin wax and polyethylene film bag for controlled release of GM pheromone, and the best suited wax/polymer bag group containing GM pheromone was selected to apply to a peach orchard in South Korea.<sup>2,3</sup>

## Experimental

Paraffin wax, beeswax, and Japan wax were melted at 60°C, and carnauba wax was melted at 90°C; GM pheromone ((Z)-8-dodecenyl acetate) (5%w/w) was added to each melted wax while stirring. Each wax mixture containing GM pheromone was poured into a wax mold, cooled slowly at room temperature, and stored at 4°C until use. The melting point of each wax mixture was measured with a differential scanning calorimeter (DSC).

Four polymer film bags (polyethylene [PE], polypropylene [PP], nylon/polyethylene [NY/PE], and polyethylene terephthalate/polyethylene [PET/PE]) were screened to select the optimal container in which to hold a wax mixture containing GM pheromone. The film thicknesses were as follows: PE and PP, 60 µm; NY/PE, 15 µm/60 µm; and PET/PE, 12 µm/60 µm. These films were used for control of GM pheromone release and protection against irregular weather.

The wax mixtures containing the GM pheromone were placed in headspace vials at 30°C. After 7 days, the quantities of GM pheromone in the air and wax matrix were measured by GC-MS. A GM pheromone release test was conducted in each wax matrix at



**Figure 1.** (A) GM insect generations in 1 year. (B) The principle of mating disruption by pheromone dispenser. The male may either fly randomly or go to a dispenser instead of finding a female.<sup>6</sup> Reproduced by permission from the Utah State University Extension IPM Program.

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30°C in an incubator for 102 days in the laboratory. The quantity of GM pheromone released was determined by measuring the quantity of GM pheromone residue in each wax mixture over time using a GC system.<sup>2,3</sup>

The Japan wax/PP film dispenser containing GM pheromone was applied as an MD dispenser to a peach orchard in Hwaseong, Kyung-gi, South Korea. The MD effect of the dispenser was assessed by equation 1 based on the captured GMs in traps.<sup>2</sup> A low number of captured males indicates effective control of GM in that plot.

$$\text{MD effect (\%)} = [1 - (X/Y)] \times 100 \quad (1)$$

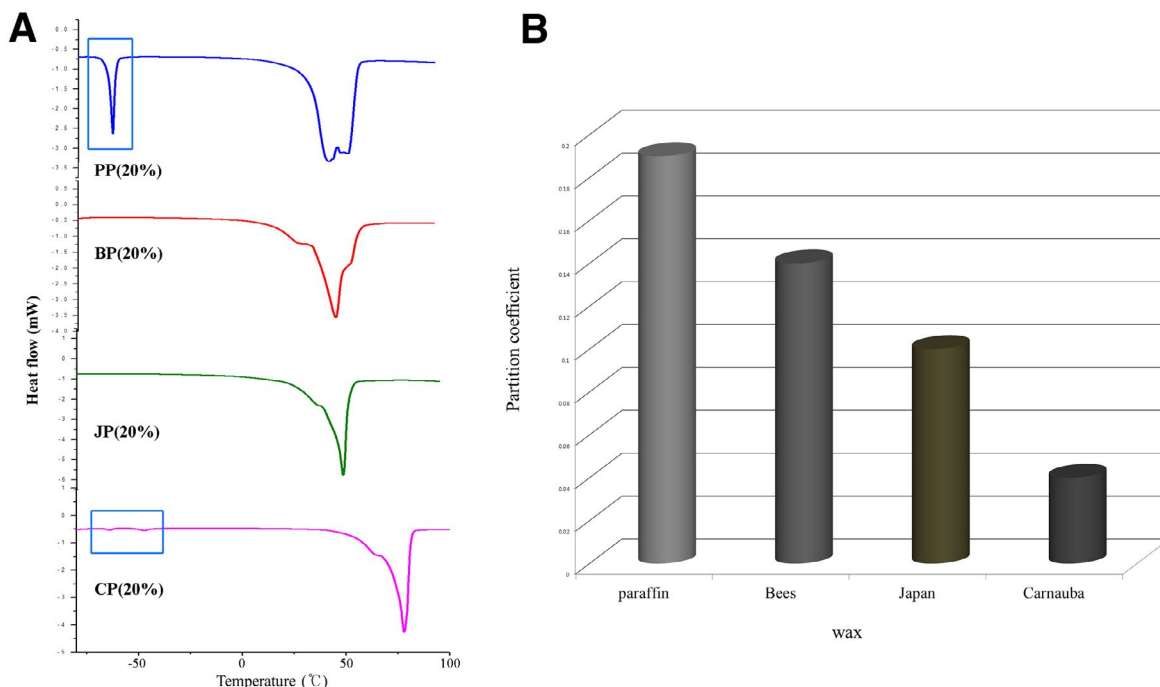
$X$  = the number of males captured in MD dispenser plots

$Y$  = the number of males captured in control plots

## Results and Discussion

The solubility of the GM pheromone with each wax and degradation of the GM pheromone in the wax mixtures were confirmed by DSC, as shown in Figure 2A.<sup>3</sup> The melting points of the paraffin wax and beeswax were 38.22–56.5 and 54.2°C, respectively, and Japan and carnauba waxes were 56 and 83.7°C, respectively. The melting point of the pure GM pheromone was –62.7°C. Paraffin wax mixture containing 5% GM pheromone showed peak separation of the GM pheromone and paraffin wax at –62.7 and 40–56°C, respectively. On the other hand, the GM pheromone was miscible in the beeswax and Japan wax mixture without any separated peaks. Although carnauba wax has similar chemical structure to GM pheromone, so that the solubility with GM pheromone was good, two small separated peaks were shown at –62.7 and –47.9°C. These two peaks were the degradation peaks of GM pheromone, which occurred because of high preparation temperature of the carnauba wax mixture, 90°C, rather than solubility.<sup>3</sup>

A headspace analysis was conducted before the GM pheromone release test, as shown in Figure 2B.<sup>3</sup> The ratios of the quantity of GM pheromone in the air/wax matrix were calculated as 0.23, 0.16, 0.11, and 0.04 for the paraffin wax, beeswax, Japan wax, and carnauba wax mixture groups, respectively. Therefore, the order of the release rate was paraffin wax > beeswax > Japan wax > carnauba wax. Figure 3 shows the GM pheromone release rate of each MD dispenser.<sup>2,3</sup> Each wax mixture containing 5% (w/w) GM pheromone was packed in four kinds of polymer film bags (PE, PP, NY/PE, and PET/PE). All wax/polymer bag groups were studied to find the optimal MD dispenser group for sustained release of GM pheromone under laboratory conditions. Female GM release the pheromone for 2–3 h/day at a rate of 8.48–25.3 ng/h.<sup>5</sup> Therefore, the suitability of the wax matrix as a dispenser was determined by comparison with GM pheromone release rates between female GM and each wax/polymer bag group. In all NY/PE and PET/PE groups, a small



**Figure 2.** (A) Differential scanning calorimetry heating curves for the paraffin wax (PP), beeswax (BP), Japan wax (JP), and carnauba wax (CP) mixtures including 20% (w/w) GM pheromone. (B) GM pheromone weight ratio in the air/wax matrix of a headspace vial at 30°C measured by gas chromatography–mass spectroscopy (each wax mixture contains 5% [w/w] GM pheromone). Reproduced by permission from the Polymer Society of Korea.<sup>3</sup>

continued

amount of GM pheromone that could not influence the MD effect was released and caged in the film bags. On the other hand, most of the wax/PP bag group showed a zero-order release rate of GM pheromone, whereas the PE group showed an irregular release rate. Thus, the PP polymer film bag was chosen as the dispenser film bag. Although both beeswax/PP and Japan wax/PP dispensers showed the same zero-order release rate per hour ( $3.1 \pm 0.3$ ), the slope of the pheromone release rate of beeswax was  $-0.590$  and Japan was  $-0.295$  in a naked wax group test, as shown in Figure 3B. From the result, Japan wax showed a more zero-order release pattern than beeswax, so that was selected as the wax material carrier with PP film. As a result, the Japan wax/PP group was applied to the peach orchard for MD of GM.

Figure 4A shows an MD dispenser (Japan wax/PP) and the control (delta trap containing GM pheromone), and the application was designed as shown in Figure 4B.<sup>2</sup> A negative control group that had only a delta trap without GM pheromone showed no male insects on the sticky sheet of the delta trap. On the other hand, the control group captured  $169 \pm 17$  male insects. In the control + MD group,  $2 \pm 1$  male insects were captured. From these results, the Japan wax/PP dispenser showed a 98% MD effect for 5 months in a peach orchard using equation 1.

## Conclusions

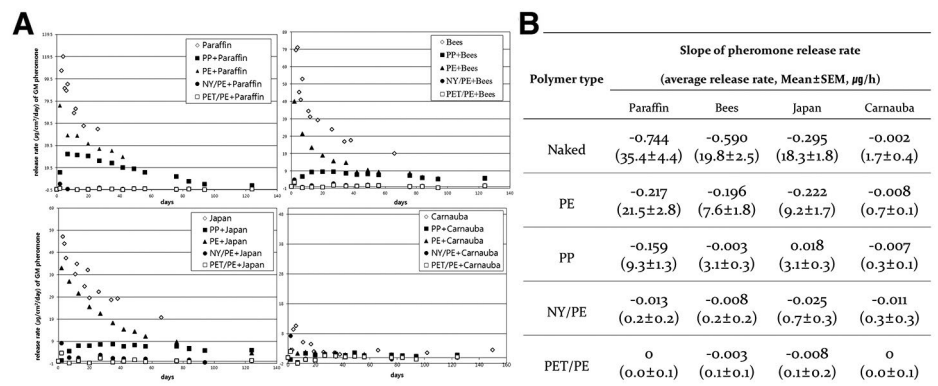
Japan wax showed good solubility with GM pheromone through a single DSC peak without any separation compared with paraffin wax. The high solubility was correlated with sustained release of the GM pheromone; thus, Japan wax showed a zero-order release pattern. The release pattern of GM pheromone in the PP bag group was also consistent with time. Therefore, the Japan wax/PP group was selected as a dispenser material for MD of GM in this study and showed an MD effect of 98% for 5 months in a peach orchard.

## Acknowledgements

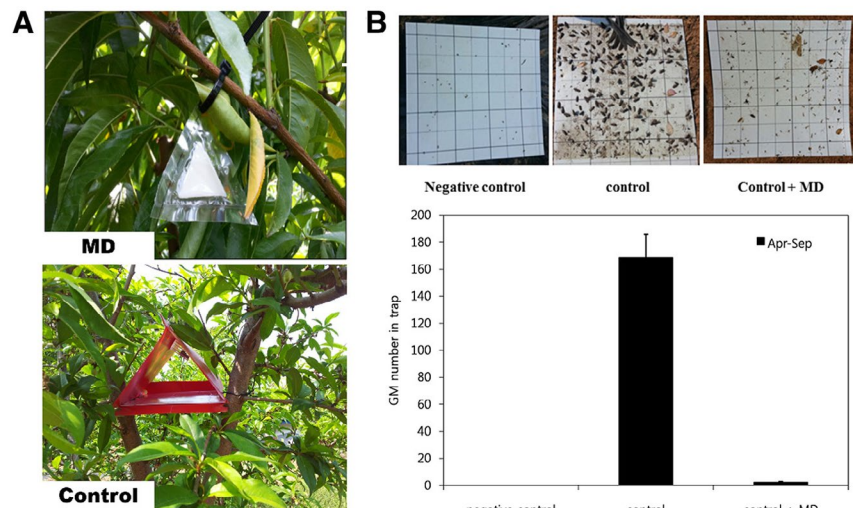
This work was carried out with the support of "Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ01021302)," Rural Development Administration, Republic of Korea.

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**Figure 3.** (A) The release rate ( $\mu\text{g}/\text{cm}^2$  per day) of GM sex pheromone according to dispenser materials at  $30^\circ\text{C}$ . (B) Slope and average of pheromone release rate of A. Reproduced in accordance with the Creative Commons attribution non-commercial license.<sup>2</sup>



**Figure 4.** Application to peach orchard. (A) Mating disruption dispenser (MD, Japan wax/PP) and the control (delta trap with GM pheromone). (B) The average trapped number (mean  $\pm$  SE) of GM male insects in the negative control (only delta trap without GM pheromone), control, and control + MD groups for 5 months. Reproduced in accordance with the Creative Commons attribution non-commercial license.<sup>2</sup>

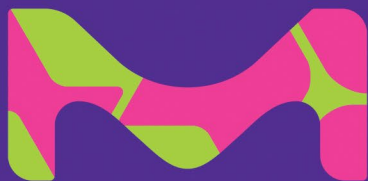




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# Report on the First Joint CRS–CoRE-Net Industry-Academia Networking Day, June 23, 2017

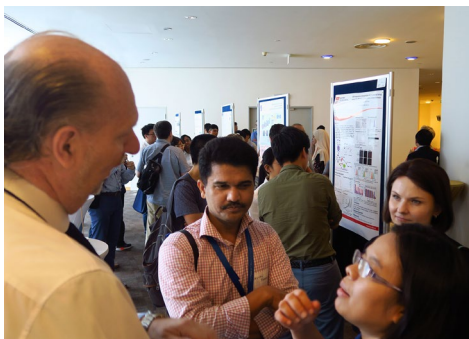
*Ben Boyd, Scientific Secretary, CRS Australian Local Chapter*



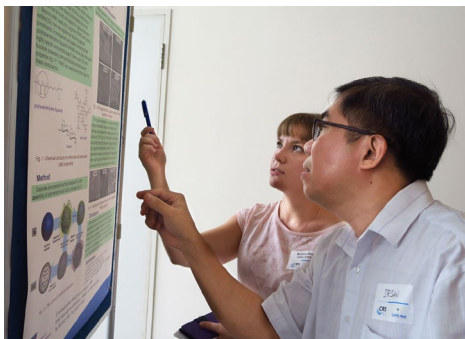
**CoRE-Net**  
Controlled Release and Encapsulation Network

There is a great opportunity in Southeast Asia to grow the network of groups active in the controlled release field. The CoRE-Net group of A\*Star focusses on bringing together companies and scientific professionals with a common interest in controlled release and encapsulation technologies by providing a networking platform for technological advancement and seeding opportunities for research cooperation. Their aim is perfectly aligned with CRS, and in recognition we joined forces and organised the First Joint CRS–CoRE-Net Industry-Academia Networking Day, jointly chaired by Ben Boyd (CRS Australian Local Chapter) and Alex van Herk (CoRE-Net/A\*Star).

The event attracted approximately 150 registrations, with one-third industry, one-third academia, and one-third A\*Star/government researchers. This was considered an outstanding success for a first one-day event, filling the available lecture space at the Biopolis Matrix Building in Singapore to capacity with both local and international attendees. The program was built around networking with only three formal speakers for the day, a poster session, and several networking sessions.



*The poster session saw lively discussion in allocated networking groups (left) and intense interrogation of students' knowledge of their work (right).*



*The audience listens and learns.*



*Alex van Herk moderates the lively panel session with the three keynote speakers on stage providing the industry, government research, and academic perspectives.*



*Keynote presenters Moitchi Kurisawa (left) and How Yee Fat (right) in action.*



*continued*

The three speakers (one academia, one A\*Star, and one industry) were Alejandro Sosnik (Technion – Israel Institute of Technology), Motoichi Kurisawa (Institute of Bioengineering and Nanotechnology, A\*STAR), and How Yee Fat (Bentz Jaz Group Singapore). Dr. Sosnik described his group's research into polymeric micellar nanocarriers, Dr. Kurisawa spoke on injectable hydrogels, and Dr. Fat described a controlled release technology used to combat the spread of malaria and dengue fever in Singapore. The students presenting posters also gave a three-minute snapshot of their poster, and judging for the best poster was difficult with such fantastic posters and presentations of their research. There could be only one winner, and Eric Saw from University of Malaya received a free student registration to the 2018 CRS Annual Meeting in New York, sponsored by CRS.

The event was completed with a roundtable discussion around a number of controversial topics at the intersection of industry, government research organizations, and academia.

The event was hugely successful, showing what can be achieved in bringing regional groups together, and has led to planning for the first Controlled Release Asia meeting, which will be held in Singapore on September 24 and 25, 2018, immediately prior to the Globalization of Pharmaceuticals Education Network (GPEN) conference. Save the dates and keep an eye out for announcements! ■



*Lively participation from audience members.*



*Students presented a “poster entrée” of three minutes, but there could only be one winner. Ben Boyd presents Eric Saw with his winner's certificate and voucher for registration to the 2018 CRS Annual Meeting in New York as first prize.*

## CRS Nordic Chapter Meeting

*Bente Steffansen,<sup>1</sup> Marika Ruponen,<sup>2</sup> Jarkko Rautio,<sup>2</sup> and Ingunn Tho<sup>3</sup>*

The annual CRS Nordic Local Chapter event of 2017 was a one-day symposium on “Drug Transporters,” which was organized back-to-back with the symposium “30-years of Drug Delivery Research – In Honour of Professor Arto Urtti’s 60<sup>th</sup> Birthday.” The Nordic Chapter event gathered 60 participants and took place in Kuopio, Finland, on June 11 in the Spa Hotel Rauhalahhti located by the beautiful Lake Kallavesi. The program was divided into a morning and an afternoon session with well-reputed invited speakers and short poster presentations from the submitted abstracts. During the Nordic Chapter symposium, 16 posters were presented.

The symposium was opened with a welcome from the local organizers by Marika Ruponen (University of Eastern Finland) and from the CRS Nordic Local Chapter by outgoing chair Ingunn Tho (University of Oslo, Norway). The new leadership from 2018 was presented, with Bente Steffansen (University of Southern Denmark) as the new chair and Christel Bergström (Uppsala University, Sweden) as vice-chair. Also, introduction of the new award established by CRS, the CRS Local Chapter Young Scientist Travel Grant, was given attention and the selection criteria explained. This award aims at promoting connectivity between the local chapters and the mother organization by providing travel grants to promising young scientists to attend the CRS Annual Meeting and present their research. The selection of awardee is to be based on the quality of the science as reflected in the research presentation in the local chapter meeting. The awardee from the CRS Nordic Local Chapter for participating in the 2018 CRS Annual Meeting was to be selected among Ph.D. students, postdocs, and young researchers presenting in the Kuopio symposium. All poster presenters in this category were given the chance to present their poster in a five-minute presentation from the podium, and the awardee was selected based on evaluation of both the short presentation and the poster.



*Discussions with the audience.*



*From the poster session.*

The first part of the scientific program was devoted to transport across the blood-brain barrier (BBB) and chaired by Marika Ruponen. Invited speaker Tetsuya Terasaki (Tohoku University, Japan) opened this part with the lecture “Retro-enantio Peptide of Transferrin Receptor Binding Peptide (D-THRre) as a Blood-Brain Barrier Permeable Stable Carrier.” He talked about how the retro-enantio peptides with their increased circulation time as compared with the parent peptide show promising results for brain delivery via receptor-mediated transcytosis utilizing the highly BBB-expressed transferrin receptor. The next speaker was Kati-Sisko Vellonen (University of Eastern Finland) with the presentation “Effect of Alzheimer’s Disease (AD) on Drug Transporters in Brain.” She introduced her study about profiling transporters and tight junction markers in AD mice models showing only minor disease-induced alterations in all studied AD animal models. The last speaker before the coffee break was Jarkko Rautio (University of Eastern Finland) with the presentation “LAT-1 Transporter as Pathway Across Blood-Brain Barrier.” He presented their research on prodrugs, such as ketoprofen-tyrosine, that are substrates for the L-type amino acid transporter (LAT-1) highly expressed on BBB. The last segment before lunch was dedicated to the short poster presentations from young researchers, and 13 enthusiastic and engaging presentations were delivered.

*continued*

<sup>1</sup> University of Southern Denmark.

<sup>2</sup> University of Eastern Finland.

<sup>3</sup> University of Oslo, Norway.

Photos: Feng Deng, Ph.D. student, University of Helsinki

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The afternoon session was devoted to clinically relevant drug transporters and chaired by Jarkko Rautio. Invited speaker Peter Swaan (University of Maryland, U.S.A.) opened this session with his lecture “Modeling and Simulation of Drug Transport: Challenges and Successes.” He talked about identifying a new class for p-glycoprotein (Pgp) drug interaction with a neural network type model by studying Pgp-drug interactions of 1,500 drugs in DrugBank. The next invited speaker was



*Winner of the CRS Nordic Chapter Young Scientist Travel Grant, Ph.D. student Eva Ramsey from University of Eastern Finland.*



*Invited speaker Peter Swaan from University of Maryland.*

Heidi Kidron (University of Helsinki), whose lecture was “Single Nucleotide Polymorphisms (SNPs) Located in the Transmembrane Regions of Breast Cancer Resistant Protein (BCRP) Impair the Expression and Transport Activity.” She lectured about performing a number of naturally occurring BCRP variants in vesicles from sf9 insect cells or human embryonic kidney (HEK) 293 cells. She showed that the efflux of BCRP probe substrates estrone-3-sulphate (E3S) and Lucifer yellow were reduced in the cells expressing variants compared with wild type (WT) BCRP and, thereby, that transmembrane regions of BCRP were sensitive to amino acid substitution. Thus, patients with these BCRP variants could suffer from unexpected pharmacokinetic events of substrate drugs. The last lecture was presented by Mikko Niemi (University of Helsinki) who talked about “Pharmacogenomics of Drug Transporters.” He showed that patients expressing the SNP of organic anion transporter (OATP)1B1-521CC could have significantly increased pravastatin plasma concentrations compared with patients with WT OATP1B1.



*Refreshments sponsored by Orion Pharma.*

Then, the incoming CRS Nordic Chapter chair Bente Steffansen awarded the CRS Local Chapter Young Scientist Travel Grant to Eva Ramsey from University of Eastern Finland for her excellent poster/short talk on “Conjunctival Drug Permeability, Employing QSPR and PK Models,” and finally closed the one-day symposium. ■

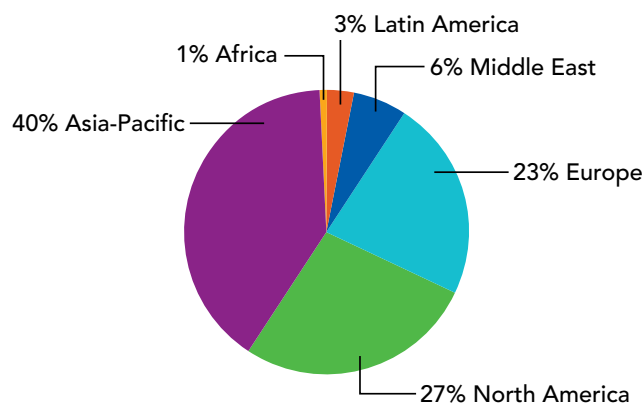


# Drug Delivery and Translational Research Update

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

## DDTR Author Satisfaction Survey

In addition to providing a forum for publishing high-quality translational drug delivery science and technology, we also aim for authors' complete satisfaction with their publishing experience in *DDTR*. Springer, the publisher of *DDTR*, carried out a survey from January to December 2016. We are pleased to see that 75% of the responders indicated that they would "definitely" consider submitting articles to *DDTR* again; the remaining 25% indicated that they would "probably" submit again, and none of the responders indicated they would not consider *DDTR* or expressed dissatisfaction with their publication experience. We are also pleased to see that *DDTR* is now accessed globally (see adjacent image). The current impact factor (2016) is 3.094.



## DDTR Special Issue: Volume 7, Issue 4, 465-607, 2017

This special themed edition of *DDTR*, "Canadian Chapter of the Controlled Release Society: Current Drug Delivery Research from Coast to Coast," introduces the reader to drug delivery research being undertaken by members of the CRS Canadian Local Chapter (<http://cc-crs.com/CRS/>) all across Canada, from Pacific coast to Atlantic coast! This special issue is structured in three sections, beginning with drug delivery research (to bone surfaces, across the blood brain barrier, peptide siRNA delivery), followed by mechanisms of drug release (from starch carriers, pluronic drug delivery systems, liposomal drug release methodology), and anchored by drug carrier and safety/efficacy research (veterinary vaccine nasal/pulmonary delivery, micelle nanocarriers, ovomucin nanoparticles, and novel doxorubicin derivatives).

## About the Guest Editors

**Michael Doschak** is an associate professor with the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta in Edmonton, Canada. His academic research program involves advanced drug delivery strategies, to effect the targeting and controlled release of drugs and peptide biologics with bone tissues, for orthopedic, orthodontic (dental), and biomaterials applications. Dr. Doschak's translational efforts in bone drug delivery have helped establish a novel platform of bone-targeting drugs, notably for the peptide hormones calcitonin and parathyroid hormone—and recently for MRI-based SPION contrast agents capable of detecting dynamic bone turnover without the use of radionuclides. He was the recipient of a 2008 Young Investigator Award from the International Society for Clinical Densitometry (ISCD) and the 2013 Teaching Excellence Award from the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta. He has served with CRS as the Canadian Chapter President (2011–2013), as a member of the Nominating Committee (2014) and the International Committee (2014–2015), and he was recently elected to the CRS Board of Scientific Advisors for a three-year term (2015–2018).



**Christine Allen** is a professor and the GlaxoSmithKline Chair in Pharmaceutics and Drug Delivery in the Leslie Dan Faculty of Pharmacy at the University of Toronto, Canada. She previously served as the Associate Dean Graduate Education and as the Associate Dean Academic. Her research is focused on the rational design and development of new materials and technologies for the delivery of drugs and contrast agents. Allen completed her doctoral research in the Department of Chemistry at McGill University and postdoctoral research in the Department of Advanced Therapeutics at the B.C. Cancer Agency. She joined University of Toronto in 2002, from Celator Pharmaceuticals Inc. (Vancouver, B.C.), where she had worked as a scientist and assistant director of materials research. She has over 100 peer-reviewed publications, numerous patent applications, and nine book chapters on both lipid and polymer-based delivery systems.

She has served on several peer-review panels for granting agencies including Canadian Institutes of Health Research (CIHR), NCIC, and NIH. She was awarded a CIHR-Rx&D Career Award (2004–2009) for her research on the design and development of technologies for cancer treatment in addition to many other awards.



**Emmanuel Ho** is currently the Leslie F. Buggie Associate Professor in the College of Pharmacy at the University of Manitoba. He is cross-appointed to the College of Medicine, Department of Immunology and the Faculty of Engineering, Department of Biomedical Engineering. Dr. Ho earned his Ph.D. in pharmaceutical sciences from the University of Toronto and was awarded an industrial postgraduate scholarship from the Natural Sciences and Engineering Research Council of Canada (NSERC). As a postdoctoral fellow at the British Columbia Cancer Research Center, he was awarded the CIHR postdoctoral fellowship along with the Michael Smith Foundation for Health Research (MSFHR) postdoctoral fellowship. His current research interests include the development of nanomedicines and medical devices for imaging, treatment, and prevention of diseases including HIV/AIDS, wound healing, and cancer. He was recently presented the 2013 Rh Award for Excellence in Research, was the recipient of the 2014 GlaxoSmithKline/Canadian Society for Pharmaceutical Sciences Early Career Award, and was awarded the 2015 Association of Faculties of Pharmacy of Canada (AFPC) New Investigator Research Award. Dr. Ho's research program is supported by grants from the Bill and Melinda Gates Foundation, CIHR, NSERC, Canada Foundation for Innovation (CFI), Research Manitoba, Manitoba Medical Service Foundation (MMSF), and Diagnostic Services Manitoba. He was recently recruited by the University of Waterloo School of Pharmacy and will begin his new position in September 2017.

*DDTR* has published 16 special issues covering different aspects of drug delivery systems and their translational applications. If you have an idea for a special issue, please contact the Editor-in-Chief, Prof. Vinod Labhasetwar, at [labhasv@ccf.org](mailto:labhasv@ccf.org). ■

## People in the News

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

### **Prof. Jennifer Dressman Joins Certara's Simcyp Scientific Advisory Board**

Business Wire: July 13, 2017 – PRINCETON, NJ, U.S.A. – Certara®, the global leader in model-informed drug development and regulatory science, today announced that Prof. Jennifer B. Dressman, Ph.D., has been appointed to the Simcyp® Scientific Advisory Board (SAB) to further strengthen its status in the biopharmaceutics field.

An expert in biopharmaceutics and a pioneer in the development of biorelevant media, Prof. Dressman is a professor of pharmaceutical technology and director of the Institute of Pharmaceutical Technology at the Johann Wolfgang Goethe University in Frankfurt, Germany.

“We are delighted that Prof. Dressman has agreed to join the Simcyp SAB. She is a visionary scientist, who uses novel biopharmaceutics tools and physiologically based pharmacokinetic models to predict the *in vivo* performance of oral drugs and dosage forms,” said Simcyp president and managing director Stephen Toon, Ph.D.

“Prof. Dressman explores how to enhance the absorption of poorly soluble drugs and modified release dosage forms through the gastrointestinal (GI) tract. She also works closely with the World Health Organization (WHO) on projects designed to improve the quality of medicines globally,” said Malcolm Rowland, Ph.D., D.Sc., Simcyp SAB Chair, professor emeritus of the Manchester School of Pharmacy at The University of Manchester, U.K., and adjunct professor in the Department of Bioengineering and Therapeutic Sciences in the Schools of Pharmacy and Medicine at the University of California, San Francisco.

Prof. Dressman's laboratory has been a designated WHO Collaborating Center since 2006.

“Prof. Dressman's research projects include forecasting food effects on drug absorption, studying the behavior of weakly basic drugs in the GI tract, and developing optimized dosage forms for GI diseases,” said Simcyp vice president of R&D Masoud Jamei, Ph.D., SMIEEE. “In addition, she led the development of biorelevant GI media that simulate the fasted and fed states *in vivo* in the late '90s.”

A recognized global authority on drug absorption, she has been an invited visiting scientist or professor at the NIHS in Tokyo, the University of Paris XI, Glaxo R&D, and the University Clermont Auvergne.

Prof. Dressman has served on the executive committee of the American Association of Pharmaceutical Scientists (AAPS) and as president of the Controlled Release Society. She is currently on the International Pharmaceutical Federation's (FIP's) executive committee of the Board of Pharmaceutical Sciences and is the chair of its Special Interest Group on Regulatory Sciences as well as its Focus Group on Biopharmaceutical Classification System (BCS) and Biowaiver.

Prof. Dressman has been honored with many research awards, including the Pharmacy Board of Victoria Prize, the C.J. Tonkin Scholarship, an Australian PostGraduate Award, the Ebert Prize, Phoenix Prize, the FIP Distinguished Scientist Award, the Nagai International Woman Pharmaceutical Scientist Award, and the Best Paper in the *European Journal of Pharmaceutics and Biopharmaceutics*. She has also been named a fellow of the AAPS, FIP, and CRS.

In addition, she is coauthor of more than 200 peer-reviewed papers, five books, and 13 patents. She has also served as corresponding author on more than 40 biowaiver monographs and as the principal advisor on more than 50 completed doctoral theses.

Prof. Dressman joins Prof. Rowland and five other esteemed members on the Simcyp SAB. They are

- Lawrence J. Lesko, Ph.D., clinical professor and director of the Center for Pharmacometrics and Systems Pharmacology in the University of Florida College of Pharmacy at Lake Nona in Orlando, FL, and former director of the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration
- J. Brian Houston, Ph.D., D.Sc., professor of drug metabolism and pharmacokinetics and co-director of the Centre for Applied Pharmacokinetic Research at the University of Manchester

*continued*



- Donald Mager, Pharm.D., Ph.D., professor of pharmaceutical sciences at the University at Buffalo, SUNY
- Geoff Tucker, Ph.D., emeritus professor of clinical pharmacology at the University of Sheffield, U.K.
- Yuichi Sugiyama, Ph.D., head of the Sugiyama Laboratory in the RIKEN Innovation Center in Tokyo and professor emeritus of the Graduate School of Pharmaceutical Sciences at The University of Tokyo.

Certara is a leading decision support technology and consulting organization committed to optimizing drug development and improving health outcomes. Certara's solutions, which span drug discovery through patient care, use the most scientifically advanced modeling and simulation technologies and regulatory strategies to increase the probability of regulatory and commercial success. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions, and key regulatory agencies. For more information, visit [www.certara.com](http://www.certara.com). ■

## Companies in the News

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

### July

#### BioLight Reports Successful Results in Phase 1/2a Clinical Trial for Glaucoma Insert

PRNewswire: July 24, 2017 – TEL-AVIV, Israel – BioLight Life Sciences Ltd. (TASE: BOLT) (“BioLight”), an emerging global ophthalmic company focused on the discovery, development, and commercialization of ophthalmic products and product candidates, announced today successful results from its glaucoma insert VS101 (“Eye-D latanoprost insert”) phase 1/2a clinical trial, which demonstrated its ability to lower intraocular pressure (“IOP”) for a 12-week period, with a favorable safety profile.

The Eye-D latanoprost insert is designed to provide sustained IOP-lowering for patients who have difficulty taking their prescribed eye drops for the treatment of glaucoma on a continuous daily basis.

BioLight’s first-in-human study, this randomized, controlled, exploratory phase 1/2a clinical trial was designed to compare three doses of its Eye-D latanoprost inserts to once-daily latanoprost eye drops. Following a simple, in-office procedure, the sustained release Eye-D latanoprost inserts were tested for 12 weeks and compared to once-daily latanoprost eye drops for the same period.

The phase 1/2a results comprise data from 77 glaucoma patients that were collected from 19 clinical centers across the United States. The data demonstrated that a single placement of the Eye-D latanoprost insert of one of the three doses provided the best sustained reduction in IOP throughout the 12 week follow up, with a positive safety profile.

Highlights of the clinical trial results include:

- Most adverse events were found to be mild and transient. No unanticipated adverse events were observed.
- Mean diurnal IOP before treatment of patients that were treated with the effective dosed insert and completed the trial was 23.5 mmHg. A sustained reduction in IOP was observed with average diurnal IOP 17.9 mmHg at the primary endpoint of 12 weeks (5.6 mmHg, 24% reduction).
- During the study, the company has gathered additional information about the procedure as well as the insert size, structure, and location, which were used to improve retention rates in patient eyes.

“Ophthalmologists today continue to struggle with finding effective solutions to the significant problem of non-adherence to the pharmaceutical treatment of patients with glaucoma,” said Dr. Howard Barnebey, M.D., who served as a principal investigator in the study. “Non-adherence is a complex problem to solve. Several therapeutic approaches that aimed to address the lack of therapy compliance and persistence have either failed or are still in development.”

Dr. Barnebey continued, “The Eye-D latanoprost insert has now successfully demonstrated effective intra-ocular pressure lowering for three months after subconjunctival placement of the insert in human eyes, and was well tolerated. This innovative insert presents a promising approach to improving therapeutic compliance, bypassing the issues of patients remembering to take medication as well as instilling it in their eyes. I am excited to participate in further development of Eye-D latanoprost insert.”

Suzana Nahum Zilberberg, BioLight’s CEO, commented, “We are very happy with the success of this clinical trial, which demonstrated that the Eye-D latanoprost insert is safe and efficacious, and intend to continue our discussions with potential strategic partners, aiming to advance the development and approval process for the Eye-D latanoprost insert, while, at the same time, promoting additional steps that will assist in optimizing the treatment for glaucoma patients. This novel technology and its first indication have the potential of becoming an important advance in the treatment of glaucoma patients.”

BioLight addresses a number of significant unmet medical needs with a pipeline of ophthalmic products and product candidates, which are in various commercial and clinical stages, including IOPtiMate™, a laser-based non-invasive surgical treatment for glaucoma; TeaRx™, a diagnostic solution that provides a multi-assay analysis of tear film constituents in order to identify one or more underlying causes of dry eye syndrome, or DES; Eye-D, an in-office insertable platform that provides for controlled release of ophthalmic medications over time; OphRx’s lyotropic liquid crystals, or LLC, a non-invasive drug delivery technology administered

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through eye drops as an alternative to current ocular delivery modalities; and LIPITEAR™, a microemulsion consisting of phospholipids and triglycerides, which forms a tear-like elastic lipid shield which is indicated for use in DES, post-operative ocular surgery (e.g., refractive surgery, cataract surgery, and corneal transplant) and corneal erosions. BioLight has also invested, through Micromedic, in innovations in cancer diagnostics.

Leading key investors are Mr. Israel Makov, chairman of Sun Pharmaceuticals, former CEO, and president of Teva Pharmaceuticals and former chairman of Given Imaging, Mr. Dilip Shanghvi, founder of Sun Pharmaceuticals, India's largest pharmaceutical company, Mr. Dan Oren, founder and CEO of Dexel Pharma, the second-largest pharmaceutical manufacturer in Israel, and Rock-One, a Hong Kong-based investment company. For more information, please visit the company's website at [www.bio-light.co.il](http://www.bio-light.co.il).

### **Braeburn and Camurus Announce Submission of NDA for Long-Acting Buprenorphine (CAM2038) for Opioid Use Disorder**

PRNewswire: July 20, 2017 – PRINCETON, NJ, U.S.A., and LUND, Sweden – Braeburn Pharmaceuticals (“Braeburn”) and Camurus (NASDAQ:STO: CAMX) today announced the completion of the rolling submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for the approval of the companies’ weekly and monthly buprenorphine depots (CAM2038) to treat opioid use disorder. Braeburn has also applied for Priority Review, which if granted could shorten the review process of CAM2038 following the FDA’s acceptance of the NDA.

“Opioid addiction is an overwhelming public health epidemic in the United States. Current daily medications for this condition are effective when taken as prescribed; however, for many patients, this can be a real challenge. Patients who do not take their medication as prescribed are ten times more likely to relapse,” said Mike Derkacz, president and CEO of Braeburn Pharmaceuticals. “If approved, patients will have access to a weekly and monthly dosing option that allows for flexible and individualized treatment from initiation on day one and throughout their recovery. This reduces the burden of daily medication, as well as the risks of misuse and diversion.”

The NDA submission for CAM2038 includes data from a comprehensive global clinical development program, evaluating 944 study participants across seven clinical trials:

- Four pharmacokinetic (PK) studies of weekly and monthly CAM2038 in healthy volunteers or patients, including also pharmacodynamic assessments.
- A phase 2 opioid blockade study demonstrating sustained blockade of drug liking and suppression of withdrawal by CAM2038 from the first day of treatment.
- A 24-week phase 3 randomized, double-blind, double-dummy study of CAM2038 against standard daily sublingual buprenorphine and included flexible dosing throughout the study period. The study met both the primary and key secondary endpoints, showing superiority for CAM2038 versus sublingual buprenorphine for the cumulative distribution function for percentage of illicit opioid-negative urine tests and self-reports.
- A 48-week phase 3 open-label, long-term safety study confirming the safety profile and long-term effectiveness of CAM2038 in new-to-treatment patients and patients switched from daily buprenorphine.

“Since the completion of our comprehensive clinical program for CAM2038, we have worked relentlessly to finalize our regulatory submissions to make these potentially treatment-transforming investigational medicines available to patients with opioid use disorder,” said Fredrik Tiberg, president and CEO, Camurus. “We are deeply appreciative of the important contributions of our investigators, nurses, and study participants, as well as the tireless efforts of our teams at Braeburn and Camurus, making this important milestone a truly collective achievement.”

This phase 3, double-blind, double-dummy study randomized 428 adults with moderate-to-severe opioid use disorder to flexible dosing with weekly and monthly CAM2038 or daily sublingual (SL) buprenorphine/naloxone (BPN/NX). Primary endpoints were non-inferiority in proportion of opioid-negative urine samples (EMA) and responder rate (FDA). A responder had no evidence of illicit opioid use at nine pre-specified time points. Superiority for the cumulative distribution function (CDF) of the percentage of opioid-negative urine samples was also evaluated.

Non-inferiority was demonstrated for both primary endpoints of non-inferiority between CAM2038 and SL BPN/NX, with a positive treatment difference of 3.4% (95% CI: –3.5 to 10.4%;  $P < 0.001$ ) for responder rate and 6.7% (95% CI: –0.1 to 13.6%;  $P < 0.001$ ) for the mean percent opioid-negative urine samples. Subsequently, following the prespecified test order, superiority of CAM2038 versus daily SL BPN/NX was demonstrated for the CDF for the percentage of illicit opioid-negative urines plus self-



reports during treatment weeks 4–24 ( $P = 0.004$ ). The safety profile of CAM2038 was generally consistent with the known safety profile of buprenorphine, with the exception of mild-to-moderate injection-site adverse events. Of the 428 enrolled patients, 128 (60.1%) in the CAM2038 group and 119 (55.3%) in the SL BPN/NX group experienced at least one adverse event, of which 70 (32.9%) and 64 (29.8%), respectively, were treatment related. Serious adverse events were reported for 5 (2.3%) of CAM2038 patients and 13 (6%) of SL BPN/NX patients. Injection site related adverse reactions were observed after 5.0% of the administered injections and in 36 (16.9%) of the 213 patients in the CAM2038 treatment group. The most common adverse reactions were injection site pain (8.9%), injection site pruritus (6.1%), and injection site erythema (4.7%). The injection site reactions were mild (78%) or moderate (22%) in severity. No serious injection site events were reported. Five cases of non-fatal drug overdoses were reported in the study (four were accidental: three heroin and one clonazepam, and one was intentional), all of which occurred in the SL BPN/NX group.

Top-line data was announced in November 2016, with further highlights presented at the annual scientific meeting of the College on Problems of Drug Dependence (CPDD) last month. Full results from the study will be presented in a scientific publication.

CAM2038 products are investigational weekly and monthly buprenorphine depot injections in development for the treatment of opioid dependence. The products are designed for flexible and individualized treatment across treatment phases, from initiation and early stabilization to longer-term maintenance therapy, providing sustained buprenorphine release and efficacy for one week and one month, respectively. Administration by healthcare professionals helps to ensure medication adherence, while potentially minimizing risks of diversion, misuse, and accidental exposure to children and teenagers. CAM2038 has been successfully evaluated in five phase 1 and 2 clinical trials, as well as a pivotal phase 3 efficacy trial and a phase 3 long-term safety trial.

CAM2038 depots are presented ready for use in prefilled syringes for weekly or monthly administration by a healthcare professional as small dose volume (about 0.6 mL) subcutaneous injection through a thin, 23-gauge needle. CAM2038 is developed for room temperature storage, avoiding the need for cold chain distribution and refrigerator storage. No mixing steps or room temperature conditioning are required prior to administration. The suite of products include dosage strengths for the once weekly that range from 8 mg to 32 mg, the once monthly injectable includes dosage strengths that range from 64 mg to 160 mg.

Braeburn is a biopharmaceutical company dedicated to delivering solutions for people living with the serious, often fatal consequences of opioid addiction. The company's mission is to advance a portfolio of next-generation therapies, with individualized dosing regimens and delivery options, to effectively address the escalating disease burden of addiction faced by patients, healthcare professionals, payers, and society. For more information about Braeburn, please visit [www.braeburnpharmaceuticals.com](http://www.braeburnpharmaceuticals.com).

Camurus is committed to developing and commercializing innovative and long-acting medicines for the treatment of severe and chronic conditions, including opioid dependence, pain, cancer, and endocrine disorders. New drug products are created based on our proprietary FluidCrystal® drug delivery technologies with the purpose of delivering improved quality of life, treatment outcomes, and resource utilization. The company's share is listed on Nasdaq Stockholm under the ticker CAMX. For more information, visit [www.camurus.com](http://www.camurus.com).

### **New Partnership Between Christiana Care's Gene Editing Institute and NovellusDx Speeds Progress Toward Personalized Cancer Medicine**

Business Wire: July 20, 2017 – WILMINGTON, DE, U.S.A. – Personalized cancer therapies are on the horizon thanks to a new genomic cancer research partnership between the Gene Editing Institute of Christiana Care Health System's Helen F. Graham Cancer Center & Research Institute and the biotechnology company NovellusDx.

The Gene Editing Institute has licensed its innovative gene editing technology to Jerusalem-based NovellusDx to improve the efficiency and speed of NovellusDx's cancer diagnostic screening tools. With the use of advanced gene editing technology, NovellusDx will be able to identify the genetic mechanism responsible for both the onset and progression of many types of cancer and determine the most effective cancer therapy. NovellusDx will pay royalties to Christiana Care for ten years for the use of its innovative gene editing technology.

"This partnership promises to redefine and transform cancer treatment by speeding progress in breakthrough personalized medicine for many forms of cancer," said Nicholas J. Petrelli, M.D., the Bank of America endowed medical director of Christiana Care's Helen F. Graham Cancer Center & Research Institute.

"This work has the potential to change the way cancer treatment is carried out," said Haim Gil-Ad, CEO of NovellusDx. "Once the genetic makeup of a patient is known, we will be able to immediately test and monitor the effect of a patient's mutations in live cells and determine the appropriate treatment for that patient."

*continued*

Today, genomic sequencing plays an ever-increasing role in cancer treatment, but the functional significance of most mutations found in a patient's DNA is unknown and so is the effect drugs have on them. NovellusDx will use the gene editing tools to help determine which drug is best for individual patients by recreating the mutations in a test system and then screening a series of known cancer drugs against those mutations to determine their efficacy.

NovellusDx has established a unique approach to identify unknown "driver" gene mutations that accelerate and facilitate cancer progression. NovellusDx receives DNA sequence information and synthesizes the individual patients' mutated genes and tests them in live cells to define the impact of each mutation on the activity of signaling pathways of the tumor and suggest the most effective therapy to the patient's physician.

A \$900,000 grant from the U.S.-Israel Binational Industrial Research and Development (BIRD) Foundation in December 2016 facilitated the Gene Editing Institute-NovellusDx partnership. The BIRD Foundation promotes collaboration between U.S. and Israeli companies in a wide range of technological fields for the purpose of joint product development.

The Gene Editing Institute of Christiana Care Health System's Helen Graham Cancer Center & Research Institute is a worldwide leader in personalized genetic medicine. Founded and led by Eric Kmiec, Ph.D., the Gene Editing Institute is unlocking the genetic mechanisms that drive cancer and that can lead to new therapies and pharmaceuticals to revolutionize cancer treatment, as well as providing instruction in the design and implementation of genetic tools. Gene editing in lung cancer research has already begun so that clinical trials can be initiated. The Gene Editing Institute is integrated into the Molecular Screening Facility at The Wistar Institute in Philadelphia, Pennsylvania, where its innovative gene-editing technologies are available to research projects at Wistar and to external users. Working with Wistar scientists, the Gene Editing Institute has begun research to conduct a clinical trial in melanoma. With funding from the U.S. National Institutes of Health, the Gene Editing Institute is partnering with Nemours to develop a gene editing strategy for the treatment of sickle cell anemia and leukemia.

NovellusDx's mission is to provide functional information about mutations and their responses to drugs so that oncologists can treat patients with precision therapies and bio-pharmaceutical companies can develop drugs more effectively. The NovellusDx approach is to monitor the functional effects of mutations and observe the effects of drugs, drug combinations, and drug candidates on the activity level caused by the mutations. NovellusDx's headquarters and research and development operations are based in Jerusalem, Israel.

### **Luye Life Sciences Expands Global Reach as New Boston R&D Center Opens**

PRNewswire: July 17, 2017 – BOSTON, MA, U.S.A. – The Luye Life Sciences Group announced today the opening of its new Boston R&D Center, the second global R&D facility set up in the United States after the one in New Jersey. The Boston R&D Center will collaborate with multiple business divisions of the Luye Life Sciences Group including Luye Pharma, Luye Medical, and Luye Diagnostics.

As an integral part of Luye Life Sciences Group's global R&D system, the newly built Boston R&D Center will focus on international R&D collaboration. In particular, joint efforts between Chinese and U.S. teams will accelerate the research and development of new drug candidates in key disease areas. The Boston R&D Center will act as an important center of excellence to internalize novel early-stage biopharmaceutical assets and disruptive drug delivery technologies.

Distinguished guests who graced the opening ceremony and spoke at the subsequent seminar included Prof. Robert S. Langer, who is the member of the National Academies of Sciences, Engineering, and Medicine ("the National Academies") and who also teaches at Massachusetts Institute of Technology (MIT); and Prof. Guangping Gao, founding director of the Hoare Gene Therapy Center of the University of Massachusetts Medical School (UMMS) and president-elect of American Society of Gene and Cell Therapy (ASGCT). Both will serve as scientific advisors for the Boston R&D Center.

"The opening of our Boston R&D Center marks another milestone in the group's exploration of pharmaceuticals," said Dr. Youxin Li, Global R&D president of Luye Pharma Group. "Building on existing R&D platforms for the drug delivery system (DDS) and Mab biosimilars, Luye Pharma is moving toward next-generation biopharmaceutical products and intelligent drug products. With Boston's leading position in the global biopharmaceutical industry, we look forward to laying a solid technical foundation through collaboration on new platforms and projects, to help ensure the sustainable pipeline development of Luye Life Sciences Group." Several biotechnology companies have already expressed their interest in working with the Boston R&D Center, tracking and analyzing a number of new early-stage drugs and technologies. These projects will effectively promote and strengthen the R&D capabilities of Luye Life Sciences Group in key areas such as cancer, schizophrenia, depression, cardiovascular anomalies, and Parkinson's disease.

As one of the major business divisions of Luye Life Sciences Group, Luye Pharma is a leading, innovation-oriented pharmaceutical company in China and also one of the first Chinese pharmaceutical companies to conduct clinical trials on the international market. Today, multiple innovative drug candidates from Luye Pharma are being studied in clinical settings for registration with the FDA.

“R&D innovation is a core engine of our globalization strategy,” said Rongbing Yang, president of Luye Pharma Group. “This Boston R&D Center allows us to further integrate our R&D resources across the world, speed up the introduction of new drugs to China, and bring our originally developed drugs to overseas markets in order to benefit more patients worldwide.”

Luye Life Sciences Group currently has operations in China, the United States, Europe, Australia, Singapore, South Korea, and Japan. Globally, the group has 15,000 employees, of which more than 60% are from outside of China. The Boston R&D Center will support the Luye Life Sciences Group to accelerate its globalization strategy and realize its vision of becoming one of the most respected global leaders in the healthcare industry through optimization and integration of global R&D resources, international talent recruitment and exchange, and cooperation on various new projects and technologies.

According to Dianbo Liu, chairman of Luye Life Sciences Group, the establishment of the Boston R&D Center is of great strategic importance. “Through this globalized platform, we look forward to building close connections with local universities, research institutes, the industry, and the financial sector,” he said. “We believe these connections will allow us to seamlessly integrate our global R&D resources with those of new partners in order to streamline innovation and realize the commercialization of high-quality biopharmaceutical products. We will continue to invest in this center, especially in terms of talent, capital, and operating processes. Ultimately, this will lead to the launch of many more innovative drugs as well as new products and technologies with real clinical value, thereby contributing to the health of all humankind.”

Founded in 1994, the Luye Life Sciences Group is committed to a mission of “professional technology serving human health.” The group is composed of three major business divisions: Luye Pharma, Luye Medical, and Luye Investment.

Luye Pharma is a leading pharmaceutical company in China, focusing on the R&D, manufacturing, and sales of innovative pharmaceutical products worldwide. Luye Pharma runs businesses in many countries and regions including China, the United States, and Europe, with over 30 marketed products. In 2016, Luye Pharma completed the acquisition of Acino’s TDS and implant business, further strengthening its R&D capability in controlled release technology. Luye Pharma currently has several new drugs with innovative delivery technologies being trialed in the United States.

Luye Medical is the medical service sector of Luye Life Sciences. Headquartered in Singapore, it is committed to becoming one of the world’s most respected leading medical companies. Luye Medical has a global presence across China, Australia, Singapore, and South Korea. It owns and operates a series of internationally renowned medical brands such as Healthe Care (Australia), AsiaMedic, Oncocare (Singapore), and Luye Ellium. Through its acquisitions and partnerships with leading healthcare organizations, Luye Medical adopts and develops world-leading technologies as well as operational and management systems. Luye Medical strives to provide integrated and high-quality healthcare services to its global customers and patients.

Luye Investment is dedicated to incubating new businesses, with a prime focus on the R&D of antibody drugs, molecular diagnostics, regenerative medicine, and health products. In 2015, Luye Investment acquired Vela Diagnostics, a Singapore-based provider of integrated molecular solutions for diagnosis. Vela Diagnostics provides equipment, tests, and data reporting solutions for real-time PCR and next-generation sequencing on an integrated platform. It will synergize with Luye Life Sciences’ current businesses to establish an entire precision medical service chain from diagnostics to treatment. In addition, Luye Investment also possesses the first human monoclonal antibody drug R&D platform and a robust pipeline of antibody drugs in research.

Founded on the R&D and manufacture of innovative drugs, led by high-end medical services, and driven by cutting-edge life sciences research, Luye Life Sciences is committed to being a full-range medical solution provider with the aim of becoming one of the most respected global leaders in the healthcare industry.

#### **BioDelivery Sciences Signs Exclusive Agreement with Purdue Pharma (Canada) for the Licensing and Distribution Rights of BELBUCA® in Canada**

PRNewswire: July 12, 2017 – RALEIGH, NC, U.S.A., and PICKERING, ON, Canada – BioDelivery Sciences International, Inc. (NASDAQ: BDSI), a specialty pharmaceutical company with a focus in pain management and addiction medicine, and Purdue Pharma (Canada) announce that they have signed an exclusive agreement for the licensing, distribution, marketing, and sale of BELBUCA® (buprenorphine buccal film) in Canada.



BELBUCA® was recently approved by Health Canada for the management of pain severe enough to require daily, continuous, long-term treatment and that is opioid-responsive and for which alternative options are inadequate. BELBUCA® incorporates BDSI's BioErodible MucoAdhesive (BEMA®) drug delivery technology and is the first and only long-acting opioid that uses novel buccal film technology to deliver buprenorphine for appropriate patients living with chronic pain.

According to the Canadian Pain Society, pain is the most common reason for seeking healthcare, with 1 in 5 Canadian adults suffering from chronic pain.

Dr. Mark A. Sirgo, president and CEO, BioDelivery Sciences International, Inc., commented: "We look forward to our partnership with Purdue Pharma (Canada) and expanding the reach of BELBUCA® to patients in Canada who are suffering from chronic pain. We are particularly enthusiastic to be partnering with a company like Purdue given their long history and commitment to pain management as well as their expertise and strong presence in the Canadian pain market. The licensing of BELBUCA® in Canada is a very important step for BioDelivery Sciences in broadening access to BELBUCA® beyond the United States, and we look forward to the introduction of the product."

Dr. Craig Landau, president and CEO, Purdue Pharma (Canada), added: "BELBUCA® provides physicians another safe and effective treatment option, when used as indicated, for Canadian patients, deemed appropriate for treatment, who suffer from long-term, chronic pain. We believe the potential benefits of this buprenorphine-containing product are significant and are enthusiastic at the opportunity to bring this therapeutic option to Canada. This agreement and the subsequent launch of Belbuca® underscores our commitment to pain patients and, more broadly, to the field of pain management."

In return for the licensing and distribution rights to BELBUCA® in Canada, BioDelivery Sciences is eligible to receive upfront and potential milestones of up to \$4.5 million CAD as well as royalties on net sales.

BioDelivery Sciences International, Inc. (NASDAQ: BDSI), is a specialty pharmaceutical company with a focus in the areas of pain management and addiction medicine. BDSI is utilizing its novel and proprietary BioErodible MucoAdhesive (BEMA®) technology and other drug delivery technologies to develop and commercialize, either on its own or in partnership with third parties, new applications of proven therapies aimed at addressing important unmet medical needs.

BDSI's area of focus is the development and commercialization of products in the areas of pain management and addiction. These are areas where BDSI believes its drug delivery technologies and products can best be applied to address critical unmet medical needs. BDSI's marketed products and those in development address serious and debilitating conditions such as breakthrough cancer pain, chronic pain, and opioid dependence. BDSI's headquarters is in Raleigh, North Carolina. For more information, please visit [www.bdsi.com](http://www.bdsi.com). For full U.S. prescribing and safety information on BELBUCA, please visit [www.belbuca.com](http://www.belbuca.com).

Purdue Pharma (Canada) is a research-based pharmaceutical company with its headquarters, R&D operations, and manufacturing located in Pickering, Ontario. The company is a leader in the research and development of medicines for the treatment of pain and central nervous system disorders (ADHD) and a growing pipeline of prescription and over the counter products. Privately held, Purdue Pharma (Canada) is independently associated with the worldwide Purdue/Napp/Mundipharma network of companies. For more information, please visit [www.purdue.ca](http://www.purdue.ca).

### **The FDA Has Accepted an Orphan Designation Request for Use of Truveta Administered Intranasally Submitted by Axiom Pharmaceuticals Inc.**

PRNewswire: July 11, 2017 – HIGH POINT, NC, U.S.A. – Axiom Pharmaceuticals Inc. ([www.axium-pharma.com](http://www.axium-pharma.com)) is a pharmaceutical company aimed at utilizing drug delivery innovations for developing improved novel formulations and alternative dosage forms of existing biologically active molecules.

Axiom is patent pending not only on the use of Truveta (lorazepam) administered intranasally but also a new intranasal administration product that is highly accurate, reproducible, and convenient for delivery of one or more predetermined unit doses of lorazepam in the form of a nasal spray delivery system. Furthermore, the system's delivery method is designed to be safe and easy, producing minimal physical discomfort and anxiety to the patient.

Subveta oral spray for transmucosal delivery is based on our waterless self-nano emulsifying formula, which is designed to prevent precipitation of the active ingredient after contact with saliva. We believe the spray provides fast onset of action and is designed to optimize drug absorption through the oral mucosa. Because the drug enters the blood stream directly, it avoids the first pass metabolism in liver and is efficiently and quickly delivered to the brain.

Axiom's pharmaceutical products are developed using highly effective technologies and demonstrated usefulness in the improvement of bioavailability and biological action of incorporated molecules. The company's product candidates address various pharmaceutical markets, including neurological disorders such as epilepsy and panic attacks, infectious diseases, and diabetes. Axiom is working closely with clinicians, patient advocate groups, and universities worldwide to identify existing health issues where Axiom's approach will be most beneficial for patient care.

The objective is to produce the relatively rapid onset of a therapeutic effect and the moderate duration of therapeutic activity, with minimal side effects and improved bioavailability.

Furthermore, the system's delivery method is designed to be safe and easy, producing minimal physical discomfort and anxiety to the patient. The medication is delivered through a small, inexpensive, manually operated, and disposable device and will be prepared under aseptic conditions; no significant residue is left in the delivery device following administration.

The FDA has accepted an orphan designation request for the intranasal lorazepam (Truveta) administered intranasally in the treatment of Lennox-Gastaut syndrome using the formulation that Axiom is developing.

Orphan drug designation will provide the following benefits: protocol assistance offered by FDA, tax credits of 50% of the clinical drug testing cost awarded upon approval, waiver of NDA/BLA application, waiver of NDA/BLA application fee (this is a \$2.2 million value), and the designation would give Axiom a seven-year market exclusivity for the sale of Truveta, among many other advantages. Axiom plans to soon be publicly traded. Keep checking the website for updates. [www.axium-pharma.com](http://www.axium-pharma.com).

### **Defymed Is Developing ExOlin®, a New Insulin Delivery Device**

Business Wire: July 10, 2017 – STRASBOURG, France – Medical technology company Defymed, based in Strasbourg, is pleased to announce the development of ExOlin®, a new insulin delivery device. Targeted at persons suffering from diabetes (type 1 diabetics and some type 2 diabetics) needing to administer insulin, this innovative medical device is being created to offer patients a better means to manage the disease, and thus a better quality of life. Following the established roadmap, this device, which shall enter the clinical phase in 2018, should be available on the market by the end of 2020.

An insulin delivery medical device, ExOlin® is composed of a biocompatible membrane, nonbiodegradable and permeable to insulin. It will be implanted into the patient's abdomen and will enable insulin to be delivered to a physiological site by simply injecting the insulin through the skin. ExOlin® has considerable advantages for patients, who can continue their normal injection methods (syringe, pen, pump, etc.) and better stabilize their blood sugar levels in the long term. Unlike pens or external pumps that deliver insulin subcutaneously, the innovative ExOlin® device delivers insulin in a much more physiologically suitable location.

"With ExOlin®, Defymed shall offer diabetic patients a more physiological approach for delivering insulin. The therapeutic effectiveness of the treatment should thus be significantly improved. The patient should also benefit from greater stability in their blood sugar levels and therefore a better quality of life," explains Dr. Séverine Sigrist, CEO and founder of Defymed.

This medical device is suitable for a wider range of applications than just diabetic patients. It could also be adapted for other applications and pathologies requiring a physiological delivery method for drugs or active ingredients.

Currently in the advanced preclinical phase, Defymed shall enter the clinical phase in 2018 with 8 patients in Europe, with aims to extend the study to a larger number of patients. By the end of 2020, Defymed aims to obtain the CE mark and then launch ExOlin® onto the market in Europe. Following this, it will pursue Food and Drug Administration (FDA) approval in the United States.

To achieve this, Defymed intends to raise 10 million euros in funds for the clinical development of ExOlin®. This should also allow Defymed to continue with the preclinical development of the MailPan® bioartificial pancreas, combined with several insulin-secreting cell candidates derived from stem cells, to enable a clinical phase to begin in the United States with the best cell(s).

As part of the development of MailPan®, Defymed benefits from the financial support of JRDF, a worldwide foundation that finances therapies for type 1 diabetes. At the end of 2016, the company also concluded a partnership agreement with Semma Therapeutics, an American biotechnology company specialized in the development of cellular therapies for the treatment of diabetes. For further information, please see <http://defymed.com/about-us>.

### **Diasome Pharmaceuticals, Inc., Receives Funding Led By Medicxi**

Business Wire: July 5, 2017 – CLEVELAND, OH, U.S.A. – Diasome Pharmaceuticals, Inc., an innovative life sciences technology company focused on the development of novel therapies for the treatment of diabetes and other metabolic conditions, announced the agreement today of new funding of up to \$30 million led by Medicxi, a leading European life sciences venture capital firm. Diasome is the first investment from Medicxi's recently announced Growth Fund I. Other investors in this round include the JDRF T1D Fund (Boston, MA), Black Beret Life Sciences, LLC (Houston, TX), and an investor group led by McDonald Partners, LLC (Cleveland, OH).

Diasome's hepatocyte directed vesicles (HDV) technology additive to commercial insulin therapies allows preferential delivery of insulin to the liver's hepatocytes. HDV-insulin is the most clinically advanced novel pre-meal insulin in the global insulin pipeline, and if approved would represent the first insulin therapy specifically designed to mimic the mealtime exposure of the liver to insulin.

"The investment by Medicxi, JDRF T1D Fund, Black Beret, and McDonald Partners represents a significant validation of Diasome's technology, and we will benefit from their track records of working with and advising successful drug development companies," said Robert Geho, CEO of Diasome.

Medicxi founding partner Dr. Michele Ollier said, "It has never been understood why insulin as a hormone replacement therapy cannot mimic the endogenous insulin activity. With HDV liver-targeted insulin, Diasome is providing a simple and elegant answer to this problem, with their preliminary human data showing that HDV makes commercial insulin more physiological, and therefore, significantly more effective. We look forward to assessing the results of the ongoing phase 2 studies." Medicxi founding partner Mr. Giuseppe Zocco added, "Diasome is the first investment from Medicxi's Growth Fund I, and the company represents a unique and disruptive opportunity in the global diabetes field. The HDV system's proprietary mechanism of action and physiology-based design are without precedent in the diabetes pharmaceutical landscape." Concurrent with Medicxi's investment, Dr. Ollier and Mr. Zocco have joined Diasome's Board of Directors.

Jonathan Behr, Ph.D., managing director of the JDRF T1D Fund, said, "JDRF knows how challenging it has been to provide patients with type 1 diabetes insulin therapies that are able to lower overall blood glucose levels while avoiding and protecting against low blood sugar, or hypoglycemic, episodes. We recognize that HDV + insulin therapy could be a significant advance for patients, and we are excited to support Diasome's team as they move forward."

Diasome will use the proceeds of this funding to continue its clinical development program and general operations, including the execution of its ongoing ISLE-1 (InSulin Liver Effect) phase 2b study of HDV-insulin in subjects with type 1 diabetes. This study is being conducted at more than 20 sites in the United States and is nearing the end of its enrollment period. Diasome has also initiated patient enrollment in two new phase 2 human (type 1 diabetes) studies of HDV + insulin within the last month.

Diasome Pharmaceuticals, Inc., is a clinical stage biopharmaceutical company focused on the clinical and commercial development of breakthrough therapies for diabetes and obesity. Based on more than 30 years of research and development in the fields of cell receptor targeting, insulin formulation, and hepatic (liver) glucose metabolism, the company's pipeline includes novel, proprietary, liver-targeted insulins for both type 1 and type 2 diabetes patients that are currently being tested in multiple human clinical trials. In addition, Diasome is developing a first-in-class oral compound for the type 2 diabetes population that is based upon new insights into normal glucose metabolism and a novel mechanism of action. For more information, visit [www.diasome.com](http://www.diasome.com).

Medicxi is based in London, Geneva, and Jersey. The company's mission is to invest across the full healthcare continuum. Medicxi was established by the former Index Ventures life sciences team. Medicxi manages the legacy life science portfolio of Index Ventures as well as the new funds launched as Medicxi, Medicxi Ventures 1 (MV1), and Medicxi Growth 1 (MG1) focusing on early-stage and late-stage investments in life sciences.

GSK, Johnson & Johnson, and Novartis, three of the world's largest pharmaceutical companies, back Medicxi along with Verily, an Alphabet company. These companies, while participating in the SABs of the funds, do not receive any preferential rights to the portfolio companies. See [www.medicxi.com](http://www.medicxi.com) for more information.



## June

### **Icon Bioscience Announces FDA Acceptance of NDA Filing for DEXYCU, a Noval Drug Therapy for Treating Inflammation Associated with Cataract Surgery**

Business Wire: June 26, 2017 – NEWARK, CA, U.S.A. – Icon Bioscience Inc. (IBI), a specialty biopharmaceutical company focused on utilizing its Verisome® drug-delivery platform to develop unique intraocular eye-care therapeutics, today announced that it has received notification from the U.S. Food and Drug Administration (FDA) that the agency has accepted for filing the company's recently submitted new drug application (NDA) for DEXYCU® (IBI-10090).

In accordance with the FDA's standard review designation, the agency has established a user fee goal date under the Prescription Drug User Fee Act (PDUFA) of February 12, 2018.

Such notification indicates that FDA has determined that the NDA for DEXYCU is sufficiently complete to permit a substantive review by the agency, and the PDUFA action date targets the potential approval of DEXYCU in early 2018.

"This is an important landmark event in advancing DEXYCU through the regulatory process into the marketplace," said David S. Tierney, M.D., Icon's president and CEO. "We look forward to working with the FDA during this review process to obtain marketing approval."

DEXYCU employs Icon's Verisome® technology to dispense a sustained-release, biodegradable formulation of the anti-inflammatory agent dexamethasone directly into the anterior chamber of the eye through a single injection administered by the physician immediately following cataract surgery. DEXYCU has been developed to help patients, in a largely elderly population, avoid noncompliance and dosing errors associated with the current standard of care, which relies on a burdensome postsurgery process of patients self-administering medicated eye-drops several times daily over a period of weeks.

Icon Bioscience, Inc., is a privately held specialty biopharmaceutical company focused on the development and commercialization of unique ophthalmic pharmaceuticals based on its patented and proprietary Verisome® extended-release drug delivery technology. The technology encompasses a broad number of related but distinct drug delivery systems capable of incorporating an extensive range of active agents, including small molecules, proteins, and monoclonal antibodies. Moreover, this drug delivery platform is a highly advanced yet elegantly formulated system for controlling the release of medication within the eye for up to a year through the administration of a single injection. The technology's exceptional versatility can support products individually formulated to meet the particular clinical requirements of a given active agent targeting a specific ophthalmic disease. For additional information, visit the Icon website at [www.iconbioscience.com](http://www.iconbioscience.com).

### **Combining Implantation of Glaukos iStent inject® Trabecular Micro-Bypass with Topical Travoprost Provides Sustained IOP Reduction and Favorable Safety Profile, According to New Study**

Business Wire: June 21, 2017 – SAN CLEMENTE, CA, U.S.A. – Glaukos Corporation (NYSE: GKOS), an ophthalmic medical technology company focused on the development and commercialization of breakthrough products and procedures designed to transform the treatment of glaucoma, today announced that a study of 53 open-angle glaucoma subjects recently published in *Clinical and Experimental Ophthalmology* showed that the iStent inject® trabecular micro-bypass, combined with topical travoprost, delivered a 35% reduction in mean intraocular pressure (IOP) to 12.9 mm Hg after 18 months of follow-up.

All subjects enrolled in this prospective, international study had open-angle glaucoma not controlled on two preoperative topical medications. The preoperative medicated mean IOP was 19.7 mm Hg. One day after implantation of two iStent inject stents in a standalone procedure, all subjects began a regimen of topical travoprost, which is a commonly prescribed ocular hypotensive medication. A total of 11 surgeons performed the procedures, and no device-related adverse events occurred through 18 months. In addition:

- At 12 months, 91% of eyes achieved a  $\geq 20\%$  decrease in IOP with the reduction of one medication.
- At 12 months, 100% of eyes achieved  $\text{IOP} \leq 18$  mm Hg, and 87% of eyes achieved  $\text{IOP} \leq 15$  mm Hg, with the reduction of one medication.
- Following medication washout at 13 months, mean unmedicated IOP decreased 33% to 16.6 mm Hg, versus 24.9 mm Hg preoperatively.

“The results of this study underscore the viability of using iStent inject together with a single postoperative prostaglandin medication to consistently manage IOP to levels in the 15 mm Hg range,” said John Berdahl, M.D., who authored the article. “What’s more, the study washouts show the independent capability of iStent inject to significantly lower IOP without any benefit from topical medications. This is important because we know that glaucoma patients often don’t adhere to topical medication treatment regimens.”

Glaukos is the study sponsor and the pioneer of Micro-Invasive Glaucoma Surgery, or MIGS. The company’s flagship MIGS device, the iStent® trabecular micro-bypass stent, was approved by the U.S. Food & Drug Administration (FDA) in 2012. Inserted through a small corneal incision made during cataract surgery, the iStent is designed to reduce IOP by restoring the natural physiological outflow of aqueous humor through the conventional pathway.

Glaukos’s next-generation iStent inject device is designed to deploy two stents into separate trabecular meshwork locations for enhanced IOP reduction and procedural ease. Two versions of the iStent inject—for combination-cataract and standalone indications—are currently being evaluated in FDA clinical trials for IOP reduction. The iStent inject is approved for use in the European Union, Canada, Australia, Brazil, and Singapore.

Glaukos is also evaluating a travoprost intraocular implant with the iDose™ delivery system in a phase II Investigational New Drug (IND) trial. Implanted during a micro-invasive procedure, the iDose is designed to continuously elute therapeutic levels of a proprietary formulation of travoprost for extended periods of time. Travoprost is designed to increase outflow primarily through the uveoscleral, or unconventional, pathway, and to a lesser extent through the conventional pathway. When the implant’s medication is depleted, the implant can be removed and replaced in a similar micro-invasive procedure.

“These results add to the growing body of peer-reviewed data that demonstrate the power of multiple trabecular bypass stents to control IOP and reduce patients’ reliance on topical medications,” said Thomas Burns, Glaukos president and chief executive officer. “Moreover, this study helps to illustrate the advantages of harnessing both the conventional and unconventional outflow pathways in order to effectively manage IOP in glaucoma patients.”

Glaukos ([www.glaukos.com](http://www.glaukos.com)) is an ophthalmic medical technology company focused on the development and commercialization of breakthrough products and procedures designed to transform the treatment of glaucoma, one of the world’s leading causes of blindness. The company pioneered Micro-Invasive Glaucoma Surgery, or MIGS, to revolutionize the traditional glaucoma treatment and management paradigm. Glaukos launched the iStent®, its first MIGS device, in the United States in July 2012 and is leveraging its platform technology to build a comprehensive and proprietary portfolio of micro-scale injectable therapies designed to address the complete range of glaucoma disease states and progression. The company believes the iStent, measuring 1.0 mm long and 0.33 mm wide, is the smallest medical device ever approved by the FDA.

### **Upon Closure of the Merger Transaction, Agrium and PotashCorp Will Become Nutrien**

PRNewswire: June 21, 2017 – SASKATOON, SK, Canada, and CALGARY, AB, Canada – Potash Corporation of Saskatchewan Inc. (PotashCorp) (TSX and NYSE: POT) and Agrium Inc. (Agrium) (TSX and NYSE: AGU) announced today that once the anticipated merger transaction closes, the new company will be named Nutrien. The new organization will be the global leader in reliable, low-cost crop nutrient production, combined with the largest agricultural retail-distribution network in the world.

The regulatory review and approval process for the merger transaction continues, and the parties expect closure of the transaction to take place in the third quarter of 2017.

Additional information on the merger between Agrium and PotashCorp can be found at the following website: [www.worldclasscropputsupplier.com](http://www.worldclasscropputsupplier.com). Information about Agrium and PotashCorp can be found under their respective corporate profiles on SEDAR at [www.sedar.com](http://www.sedar.com) or on EDGAR at [www.sec.gov](http://www.sec.gov), respective websites at [www.agrium.com](http://www.agrium.com) and [www.potashcorp.com](http://www.potashcorp.com), or by contacting the representatives below.

PotashCorp is the world’s largest crop nutrient company and plays an integral role in global food production. The company produces the three essential nutrients required to help farmers grow healthier, more abundant crops. With global population rising and diets improving in developing countries, these nutrients offer a responsible and practical solution to meeting the long-term demand for food. PotashCorp is the largest producer, by capacity, of potash and one of the largest producers of nitrogen and phosphate. While agriculture is its primary market, the company also produces products for animal nutrition and industrial uses. Common shares of Potash Corporation of Saskatchewan Inc. are listed on the Toronto Stock Exchange and the New York Stock Exchange.

Agrium Inc. is a major global producer and distributor of agricultural products, services, and solutions. Agrium produces nitrogen, potash, and phosphate fertilizers, with a combined wholesale nutrient capacity of approximately eleven million tonnes and with significant competitive advantages across our product lines. We supply key products and services directly to growers, including crop nutrients, crop protection, seed, as well as agronomic and application services, thereby helping growers to meet the ever-growing global demand for food and fiber. Agrium retail-distribution has an unmatched network of approximately 1,500 facilities and over 3,300 crop consultants who provide advice and products to our grower customers to help them increase their yields and returns on hundreds of different crops. With a focus on sustainability, the company strives to improve the communities in which it operates through safety, education, environmental improvement, and new technologies such as the development of precision agriculture and controlled release nutrient products. Agrium is focused on driving operational excellence across our businesses, pursuing value-enhancing growth opportunities and returning capital to shareholders. For more information, visit [www.agrium.com](http://www.agrium.com).

### **NanoSphere Health Sciences Signs Binding Merger Agreement for 100% Acquisition by Corazon Gold Corp.**

Business Wire: June 20, 2017 – DENVER, CO, U.S.A. – NanoSphere Health Sciences, LLC, developer of the innovative, industry-first, patent-pending NanoSphere Delivery System™ for cannabis and other pharmaceuticals, today announces that it has signed a binding merger agreement with Corazon Gold Corp. (TSX-V: CGW) for 100 percent acquisition of NanoSphere's issued and outstanding shares.

This move is pivotal to NanoSphere's strategy to expand nationally and internationally, getting in on the ground floor of the Canadian cannabis market following new legislation.

While medical marijuana has been legal in Canada since 2001, in April, the government filed an act to amend the Controlled Drugs and Substances Act, with the goal of legalizing adult recreational cannabis use by July 2018. As such, Deloitte estimates the base retail value of the Canadian market alone to be upwards of \$8 billion. On top of that, Arcview projects the legal marijuana market in the United States will hit \$20.6 billion in revenue by 2020.

"This alignment represents a significant opportunity to take advantage of the nascent Canadian and burgeoning U.S. cannabis markets," said Robert Sutton, chairman, NanoSphere Health Sciences. "Across the board, as more countries and states legalize marijuana for recreational and medical use, we are seeing an increased demand for more precise and efficient cannabis delivery methods to help relieve pain and anxiety. NanoSphere's technology can provide exactly that, addressing many issues faced with traditional delivery methods (like inhalation and ingestion). We look forward to being able provide new customers with a more sophisticated, safer alternative."

The NanoSphere Delivery System™ for cannabis pioneers standardized, precision, microlitered dosages by intra-oral, intra-nasal, and transdermal administration. Recent pharmacokinetic testing confirmed the rapid entrance of THC into the blood stream when using NanoSphere products. Onset occurs within ten minutes, compared to an hour or more with standard ingested THC. The testing also demonstrated significantly higher blood concentrations, greater bioavailability, and longer circulation half-life within the human body compared to ingested THC and oral mucosal spray.

Corazon commissioned an extensive and independent company valuation report of NanoSphere Health Sciences' patent-pending technologies and intellectual property (IP) based on its current application in the cannabis space. This independent report concluded based on the potential of the company's technology, the valuation of the NanoSphere cannabis division alone is approximately \$24 million CAD.

The terms of the acquisition are that Corazon will issue 40,000,000 common shares upon closing and an additional 19,000,000 shares upon initial commercialization of NanoSphere's products. All common shares issued at a deemed price of \$0.50 per common share to existing shareholders of NanoSphere. Corazon also intends to complete a financing of \$7,000,000 CAD, for which the terms will be announced in short order.

NanoSphere is also pleased to announce that it is in the process of submitting a listing statement to the Canadian Securities Exchange (CSE). This move provides greater flexibility to the company while developing revenue streams and will greatly reduce initial listing and on-going public company costs.

Headquartered in Denver, Colorado, NanoSphere Health Sciences is a biotechnology firm specializing in the creation of NanoSphere Delivery System™ platform for the supplement, nutraceutical, over-the-counter medications, pharmaceutical, animal health, and cannabis industries and beyond. Its patent-pending NanoSphere Delivery System™ represents one of the most important developments for advancing the non-invasive delivery of biological agents in over 25 years. [www.nanospherehealth.com](http://www.nanospherehealth.com).

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### **Ligand's Partner Melinta Therapeutics Announces U.S. FDA Approval of Baxdela™ (Delafloxacin) for Acute Bacterial Skin and Skin Structure Infections (ABSSSI)**

Business Wire: June 20, 2017 – SAN DIEGO, CA, U.S.A. – Ligand Pharmaceuticals Incorporated (NASDAQ: LGND) announces that partner Melinta Therapeutics, a privately held company focused on discovering, developing, and commercializing novel antibiotics to treat serious bacterial infections, announced yesterday that the U.S. Food and Drug Administration (FDA) has approved Baxdela™ (delafloxacin), indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible bacteria. Baxdela is a fluoroquinolone that exhibits activity against both gram-positive and gram-negative pathogens, including MRSA (methicillin-resistant *Staphylococcus aureus*), and is available in both intravenous (IV) and oral formulations. Baxdela IV utilizes Ligand's Captisol® technology. As a result of the approval, Ligand has earned a \$1.5 million milestone payment and will earn a 2.5% royalty on Baxdela IV sales.

"We congratulate Melinta for this first regulatory approval for Baxdela," said John Higgins, chief executive officer of Ligand. "Melinta has been an excellent partner, efficiently managing their clinical development work and collaboratively interfacing with Ligand's technical team in successfully leveraging our Captisol technology for the IV formulation of Baxdela. We have identified this program as one of Ligand's Big Six partnered pipeline assets given its medical importance and stage of development. This approval and Melinta's recently announced commercial and co-development agreement with Menarini Group position Baxdela for global commercial success."

"The approximately 3 million patients hospitalized each year in the United States with ABSSSI often present treatment challenges owing to their underlying medical conditions, making optimal antibiotic selection difficult. Baxdela provides a treatment option for adult patients with ABSSSI based on its coverage spectrum, IV and oral dosing flexibility, efficacy, and safety profile," said Eugene Sun, M.D., CEO of Melinta. "The approval of Baxdela demonstrates FDA's commitment to making new and effective antibiotics available to address unmet needs for hospitalized ABSSSI patients."

"Antibiotic resistance is a growing concern, and physicians need more tools in the fight against this threat to modern medicine. Approval of new therapies like Baxdela, which is effective against MRSA and other serious pathogens, provides physicians another option in addressing the challenges of ABSSSI patients," said Dr. David Hooper, professor of medicine, Harvard University, and chief of infection control, associate chief, Division of Infectious Diseases, Massachusetts General Hospital.

The Baxdela New Drug Application (NDA) approvals were supported by two phase 3 studies in patients with ABSSSI, demonstrating that IV and oral Baxdela monotherapy was statistically non-inferior to the combination of vancomycin plus aztreonam at the FDA primary endpoint of early clinical response at 48–72 hours. Baxdela was well tolerated with a 0.9% discontinuation rate in the phase 3 studies due to adverse events. In addition, Baxdela has not shown any potential for QT prolongation or phototoxicity in definitive clinical studies. There have been no signals of adverse effects on liver function, kidney function, or glucose regulation in controlled clinical studies. The 450 mg tablet is bioequivalent (area under the curve) to, and interchangeable with the 300 mg IV dose, and can be dosed without regard to food. There are no anticipated drug-drug interactions with delafloxacin other than co-administration with chelating agents, such as antacids.

Baxdela (delafloxacin) tablets and intravenous injection are approved for the treatment of ABSSSI (acute bacterial skin and skin structure infections). Baxdela was given priority review by the FDA due to its designation as a Qualified Infectious Disease Product (QIDP) under the Generating Antibiotic Incentives Now (GAIN) Act of 2012. The QIDP designation qualifies Baxdela for certain incentives related to the development of new antibiotics, including a five-year extension of any non-patent exclusivity period awarded to the drug.

### **Achelios Therapeutics Concludes Successful Type C Meeting with FDA Regarding Its Lead Product, TOPOFEN™, for Prevention and Treatment of Migraine**

PRNewswire: June 14, 2017 – CHAPEL HILL, NC, U.S.A. – Achelios Therapeutics, a privately held pharmaceutical development company focused on innovative topical drug delivery technologies, announced today it has completed a Type C meeting with the FDA regarding a path to approval for TOPOFEN™ in acute and chronic migraine.

Achelios' recently completed phase 2a study demonstrated that the topical application of a well-known non-steroidal anti-inflammatory drug (NSAID) to facial areas innervated by trigeminal nerve branches may be a safe and effective alternative treatment for patients suffering from acute migraine. For the Type C meeting Achelios sought confirmation of the requirements for phase 3 and New Drug Application (NDA) submission. Currently there are no approved topical NSAIDs indicated for the treatment of migraine.



“This new FDA guidance confirms our previous interactions with the agency, provides for a streamlined development path to approval, and is consistent with our previous guidance and with the FDA regulations for a 505(b) (2) NDA application,” said John G. Fort, M.D., M.B.A., the company’s chief medical officer. “Based on the streamlined clinical trial requirements, Achelios will be able to achieve an NDA filing in a relatively quick and cost-effective manner compared to what is typically required for a new chemical entity (NCE).”

Wolfgang Liedtke, M.D., Ph.D., from Duke University is a member of the team that conducted the research and a paid advisor to Achelios. Liedtke, a tenured professor of neurology, anesthesiology, and neurobiology and attending physician at Duke University, said, “The results of the study are encouraging, and those of us who treat migraine think it may lead to a meaningful alternative treatment for a substantial number of migraineurs. This study showed that it may be possible to affect severe migraine, which can be a debilitating neurological pain condition, with a topical application to facial trigeminal nerve endings.”

Crist Frangakis, Ph.D., the company’s president and CEO, said, “TOPOFEN™ represents a novel approach for the acute treatment and prophylaxis in chronic migraine, with unique benefits for the patient and importantly, given the intellectual property that has been both filed and granted, a patent-protected opportunity for a potential partner. We believe TOPOFEN™ provides great value given its low required development costs and accelerated time to market relative to other potential new therapies. We also see TOPOFEN™ as having tremendous value for patients outside of migraine, given the potential for additional indications such as temporomandibular joint disease (TMJD), post-operative inflammatory pain, chemotherapy-induced neuropathic pain (CINP) and joint arthritis pain.”

TOPOFEN™ is a proprietary gel formulation of ketoprofen. TOPOFEN’s™ beneficial effect is mediated through its regulation of neuronal CGRP release by its ability to prevent the generation of prostaglandins to suppress the neurogenic inflammatory response. In addition to migraine treatment, TOPOFEN™ has the potential for use in a variety of pain disorders including TMJD, post-operative inflammatory pain, CINP, and joint arthritic pain.

#### **Ensysce Biosciences Inc. Attending NIH Conference: Cutting Edge Science Meeting Series to End the Opioid Crisis: Development of Safe, Effective, Non-Addictive Pain Treatments**

Business Wire: June 12, 2017 – SAN DIEGO, CA, U.S.A. – Ensysce Biosciences Inc. has been invited to attend conference Cutting Edge Science Meeting Series to End the Opioid Crisis: Development of Safe, Effective, Non-Addictive Pain Treatments taking place June 16, 2017, at the National Institutes of Health (NIH) Campus, Bethesda, MD. This conference is one of three that are planned to accelerate research to help end the opioid crisis in the major areas of (1) new and innovative medications/biologics to treat opioid addiction and for overdose prevention/reversal; (2) safe, effective, and non-addictive strategies to manage chronic pain; and (3) neurobiology of chronic pain. The NIH is bringing together some of the most creative and innovative experts from industry and academia to help identify the scientific strategies of greatest potential to expedite solutions for the opioid problem. The planned vigorous brainstorming sessions will provide opportunities to identify new approaches and recruit additional expertise to accelerate progress. Dr. William K. Schmidt, chief medical officer of Ensysce, will participate. Ensysce has been instrumental in developing highly novel opioid prodrug products that are unique in the industry. These BIO-MD™ abuse deterrent prodrugs are only effective if taken orally and activated through a two-step enzymatic process. The technology removes abuse by nasal or intravenous routes and will not activate if chewed. The lead product in development, PF614, has recently completed a phase 1 clinical study that demonstrated its safety and extended release pharmacokinetic profile with a 12 hour half-life, almost twice that of other marketed products. Additionally, Ensysce has addressed the problem of overdose abuse with its MPAR™ (Multi-Pill Abuse Resistance) overdose protection technology that combines BIO-MD products with inhibitors that prevent activation when larger than prescribed doses are ingested.

Ensysce Biosciences is an integrated drug delivery company for both small and large molecules. The BIO-MDTM and MPAR™ overdose resistant platforms eliminate the ability to abuse opioid products by the non-oral route, the fastest growing drug problem in the United States leading to billions in healthcare costs annually. The technology, with a worldwide intellectual patent protection, has been successfully validated in phase 1 studies of the BIO-MDTM hydromorphone prodrug, PF329, and the oxycodone prodrug, PF614.

#### **Scientifically Advanced Delivery Technology in Sleep Management Debuts at SLEEP 2017 with Clinical Data Showing REMfresh®, the First and Only Continuous Release and Absorption Melatonin, Helps Maintain Sleep for up to 7 Hours**

PRNewswire: June 5, 2017 – BOSTON, MA, U.S.A. – Landmark clinical data presented today highlight a scientific breakthrough in the management of sleep with a drug-free, non-prescription sleep product, REMfresh®, the first and only, continuous release and absorption melatonin (CRA-melatonin) to mimic the body’s own 7-hour Mesa Wave™, a natural pattern of melatonin blood levels during a normal night’s sleep cycle. The study demonstrated the continuous release and absorption of 99% ultra-pure melatonin in REMfresh® (CRA-melatonin) was designed to induce sleep onset and provide continuous, lasting restorative sleep over 7 hours. The

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scientifically advanced, patented formulation, called Ion Powered Pump (IPP™) technology, replicates the way in which the body naturally releases and absorbs melatonin, unlike conventional melatonin sleep products. Since REMfresh® is not a drug, there is no drug hangover.

The data are being presented in three posters on Sunday, June 4, and Tuesday, June 6, during SLEEP 2017, the 31st Annual Meeting of the Associated Professional Sleep Societies LLC (APSS). The meeting is a joint meeting of the American Academy of Sleep Medicine (AASM) and the Sleep Research Society (SRS).

“These results represent an unparalleled breakthrough in drug-free sleep maintenance therapy that physicians and their patients have been waiting for,” said David C. Brodner, M.D., a leading sleep specialist who is double board-certified in otolaryngology–head and neck surgery and sleep medicine, founder and principal physician at the Center for Sinus, Allergy, and Sleep Wellness, in Palm Beach Country, Florida, and senior medical advisor for Physician’s Seal, LLC®. “Melatonin products have been used primarily as a chronobiotic to address sleep disorders associated with abnormal timing of the circadian system, such as jet lag and shift work, but that has now changed. With its patented IPP™ delivery system that mimics the body’s own natural sleep pattern, REMfresh® may allow more individuals having trouble sleeping to experience drug-free, consistent, restorative sleep and have an improved quality of life.”

The findings are based on REMAKT™ (REM Absorption Kinetics Trial), a U.S.-based randomized, crossover pharmacokinetic (PK) evaluation study in healthy, non-smoking adults that compared REMfresh® (CRA-melatonin) with a market-leading, immediate-release melatonin (IR-melatonin). The study found that melatonin levels with REMfresh® exceeded the targeted sleep maintenance threshold for a median of 6.7 hours, compared with 3.7 hours with the leading IR-melatonin. Conversely, the levels of the market-leading IR-melatonin formulation dramatically increased 23 times greater than the targeted levels of exogenous melatonin for sleep maintenance and had a rapid decline in serum levels that did not allow melatonin levels to be maintained beyond 4 hours.

Analysis presented at SLEEP 2017 showed that REMfresh® (CRA-melatonin) builds upon the body of evidence from prolonged-release melatonin (PR-M), which demonstrated in well-conducted, placebo-controlled studies, statistically significant improvement in sleep quality, morning alertness, sleep latency, and quality of life in patients aged 55 years and older compared with placebo. REMfresh® (CRA-melatonin) was designed to overcome the challenges of absorption in the intestines, thereby extending the continual and gradual release pattern of melatonin through the night (known as the Mesa Wave™, a flat-topped hill with steep sides). There was a faster time to Cmax, which is anticipated to result in improved sleep onset, while the extended median plateau time to 6.7 hours and rapid fall-off in plasma levels at the end of the Mesa Wave™ may help to improve sleep maintenance and morning alertness.

Chronic sleep and wakefulness disorders affect an estimated 50 to 70 million Americans, and long-term sleep deprivation has been associated with negative health consequences, including an increased risk of diabetes, hypertension, heart attack, stroke, obesity, and depression.

Sleep/wake cycles are regulated by melatonin, levels of which normally begin to rise in the mid- to late evening and remain high for the majority of the night. Levels begin to decline towards early morning, as the body’s wake cycle is triggered. Melatonin levels typically decline with age, with a significant decrease after age 40.

The REMAKT™ data will be submitted for peer review and publication in a medical journal.

Physician’s Seal® is the innovator of REMfresh®, the first and only continuous release and absorption, 99% ultra-pure melatonin (CRA-melatonin) that mimics the way the body naturally releases and maintains melatonin over a 7-hour period. Physician’s Seal®, founded in 2015, is a privately held company based in Boca Raton, Florida. It is committed to bringing cutting-edge life science applications to doctors and their patients. For more information, visit [www.remfresh.com](http://www.remfresh.com).

### **Aequus Pharmaceuticals and CDRD Announce Research Collaboration to Improve Cannabinoid-Based Therapeutics**

Business Wire: June 1, 2017 – VANCOUVER, BC, Canada – Aequus Pharmaceuticals Inc. (TSX-V: AQS, OTCQB: AQSZF) (“Aequus”) a specialty pharmaceutical company with expertise in drug delivery and clinical development, and the Centre For Drug Research and Development (“CDRD”), Canada’s national drug development and commercialization centre, announced a broad research collaboration to establish pre-clinical safety and efficacy of select cannabinoid-based therapeutics targeting neurological movement disorders including epilepsy, multiple sclerosis, Parkinson’s disease, and Huntington’s disease.

Aequus has initiated a research program of cannabinoid-based therapeutics targeting neurological disorders. In 2016, Health Canada provided patients in Canada the ability to access cannabis for medical purposes when recommended by their physician. There are insufficient data, however, for proper therapeutic treatment protocols regarding the proper dosage and frequency for patients dealing with a wide variety of symptoms and disease areas. Aequus recently published a survey that confirms the medical need for improved clinical trial data supporting safety and efficacy of medical cannabis, reliability of dose delivery systems, high quality data collection tracking real-world clinical outcomes, physician education, and quality controlled ingredients.

The goal of the Aequus/CDRD partnership is to address many of these deficiencies. The preclinical studies, including *in vitro* and *in vivo* toxicology, pharmacology, and formulation optimization in relevant disease models, will be conducted at CDRD's facilities in Vancouver, BC, pending Health Canada approvals. This initial project leverages CDRD's expertise in pre-clinical development and target validation for new products, and demonstrates CDRD's ongoing engagement with life sciences companies in the Canadian marketplace. Products advanced through the collaboration will be commercialized by Aequus.

Aequus intends to leverage its expertise in developing and commercializing regulated prescription therapeutics and will work with sophisticated third party partners like the CDRD to develop pharmaceutical grade products for patients seeking the use of optimized delivery versions of clinically validated formulations of medical cannabis.

"This is an exciting step as we advance toward our goal of providing patients and physicians with clinically validated cannabinoid-containing treatments delivered in a more precise and optimized manner than inhaling or ingesting, the most common current methods of delivery," said Doug Janzen. "We view the clinician community as being important stakeholders, and we are excited to work with a world-class drug research and development organization like CDRD as we strive to provide the medical community with validated and improved alternatives to existing products. Together our two organizations have proven expertise in taking drugs from discovery and preclinical trials all the way through clinical trials to regulatory launch and commercial sales—a potent combination for advancing cannabinoid-containing therapeutics for neurologic movement disorders."

Gordon McCauley, CDRD's president and CEO, commented, "Our partnership with Aequus is a great example of the work we do with biotech across the country. There is a clear unmet medical need in the area of medical cannabinoid research and development where CDRD and Aequus can collaborate and share their respective expertise that could lead to new cannabinoid therapeutics and a pathway to clinical trials, particularly in neurological movement disorders."

CDRD is Canada's national drug development and commercialization centre working in partnership with academia, industry, government, and foundations. CDRD provides the specialized expertise and infrastructure to identify, validate, and advance promising discoveries, and transform them into commercially viable investment opportunities for the private sector—and ultimately into new therapies for patients. Canada's Networks of Centres of Excellence Program has recognized CDRD as a Centre of Excellence for Commercialization and Research (CECR). [www.cdrd.ca](http://www.cdrd.ca).

Aequus Pharmaceuticals Inc. (TSX-V: AQS, OTCQB: AQSZF) is a growing specialty pharmaceutical company focused on developing and commercializing high quality, differentiated products. Aequus's development stage pipeline includes several products in neurology and psychiatry with a goal of addressing the need for improved medication adherence through enhanced delivery systems. Aequus intends to commercialize its internal programs in Canada alongside its current portfolio of marketed established medicines and will look to form strategic partnerships that would maximize the reach of its product candidates worldwide. Aequus plans to build on its Canadian commercial platform through the launch of additional products that are either created internally or brought in through an acquisition or license, remaining focused on highly specialized therapeutic areas. For further information, please visit [www.aequuspharma.ca](http://www.aequuspharma.ca).

## May

### Vetter and Microdermics Enter into a Strategic Cooperation Agreement to Develop Innovative Microneedle Drug Delivery Systems

Business Wire: May 31, 2017 – RAVENSBURG, Germany, and VANCOUVER, BC, Canada – Vetter, a leading and innovative provider of aseptic prefilled drug delivery systems, and Microdermics Inc., a Vancouver-based medical device company developing a novel hollow, metal microneedle drug and vaccine delivery system, today announced that they have entered into a strategic cooperation agreement.

The market in novel alternatives to needle injections is forecasted to grow rapidly, reaching in excess of 480 million units by 2030 (Roots Analysis report). Microneedles are a novel technology that can offer promising advantages as an alternative to classical needle injections and other routes of administration, mainly in reducing the injectable dose needed to trigger an immune response and accelerating drug absorption by the body. The roadblocks to commercialization are mainly due to limited investment in scalable aseptic manufacture at the later phases of development. To overcome this hurdle the two companies have joined forces to leverage the expertise of both firms and enable late-stage process development and device manufacture on a commercial scale. Microdermics microneedle technology is commercially scalable and capable of pain-free injections into the pharmacokinetically beneficial intradermal space, providing improved comfort and treatment to patients. Microdermics has successfully demonstrated the initial safety of its microneedle system and is planning phase 1 human clinical trials for vaccine and therapeutic delivery, to be initiated in 2017.

As a leading contract development and manufacturing organization (CDMO), Vetter offers its customers a beneficial service through a combination of device development and associated drug product manufacturing and packaging services. Vetter tries to integrate its customers in technological advancements as early as possible. By continuously participating in market development in innovative and proactive ways, the company is committed to acting with the goal of increasing patient convenience and compliance in mind.

Microdermics has developed a novel commercially scalable, low-cost, customizable, metal, hollow microneedle platform that provides efficient delivery of vaccines and biologics—addressing the global reliance on the 160-year-old hypodermic needle and the economic and health implications associated with widespread needle phobia. The company's phase 1 clinical trials to validate the effectiveness and reliability of intradermal delivery are expected to initiate in 2017. Microdermics will focus product development and clinical activities on new delivery methods for existing commercial products, providing innovative methods for partners to differentiate via a novel intradermal delivery system, as well as pursue product life cycle extensions.

“We are very happy to enter into this agreement with Microdermics, and we are excited by the initial experience of cooperation and entrepreneurial spirit we have established with key individuals at this company,” said Dr. Claus Feussner, Vetter's senior vice president, development service. “We believe that microneedles are a particularly innovative technology and may prove to be a promising future alternative for selected areas of drug delivery.”

“Microdermics is extremely excited to work with a world-class partner like Vetter, since our strategic interests align, and their decades of experience and innovation in the fill and finish segment will enable us to accelerate our commercialization strategy. Vetter's vast experience with a wide variety of drug substances provides us with an invaluable opportunity for a successful development path for our microneedle drug delivery technology,” said Grant Campy, president and CEO of Microdermics. “While our individual companies differ in size, experience, and structure, we are fully aligned in our vision to achieve the best possible patient convenience with our product offerings,” said Prof. Boris Stoeber, Microdermics' cofounder and chief technology officer.

Vetter is a global leader in the fill and finish of aseptically prefilled syringe systems, cartridges, and vials. Headquartered in Ravensburg, Germany, the company operates production facilities in Germany and the United States, as well as sales offices in Singapore and Tokyo, Japan. The contract development and manufacturing organization (CDMO) is an innovative solution provider serving small, midsize, and the top 10 (bio-) pharmaceutical companies. Its portfolio spans state-of-the-art manufacturing from early clinical development through commercial filling and final packaging of parenteral drugs. Known for quality, the company of approximately 4,300 employees offers a foundation of experience spanning more than 35 years, including dozens of customer product approvals for novel compounds. More than 80% of Vetter's active projects are biologics, and Vetter currently manufactures five of the world's top 10. The CDMO is also committed to patient safety and compliance with user-friendly solutions such as Vetter-Ject®, as well as its dual-chamber syringe Vetter Lyo-Ject® and cartridge system V-LK®. Visit [www.vetter-pharma.com](http://www.vetter-pharma.com).

Microdermics is a Vancouver-based medical device company (with a business office in San Francisco) revolutionizing the biopharmaceutical market for both patients and healthcare practitioners. As the only company with a low-cost, scalable, hollow, metal microneedle, Microdermics eliminates the danger of accidental needle sticks caused by hypodermic needles and addresses the global health impact related to needle phobia. Microdermics will leverage its proprietary and innovative delivery system across a spectrum of biopharmaceuticals, including a new market for biosimilars, providing biopharmaceutical companies with a means of differentiating themselves from their competitors as well as securing product life cycle extensions. Learn more at [www.microdermics.com](http://www.microdermics.com).

### **BIOCORP Signs an Industrialization Contract with Virbac**

Business Wire: May 29, 2017 – ISSOIRE, France – BIOCORP (FR0012788065 – ALCOR/PEA-PME eligible), a French company specializing in the development and manufacturing of medical devices and smart-drug delivery systems, announced today the signature of an industrialization contract with Virbac, the 7th veterinary company worldwide.



BIOCORP, whose expertise and know-how are well-renowned, is thereby closing a deal in line with its strategy of creating new opportunities and manufacturing programs through specific developments implemented since 2015 (project-based services using BIOCORP's expertise). Virbac Group, a company dedicated to animal health, employs over 4,800 people and has a global presence with subsidiaries in 31 countries, production centers in 11 countries, and R&D centers on 5 continents.

The investment deal was closed after a 24-month collaboration between BIOCORP and Virbac for the development of a delivery device adapted to the needs of the veterinary laboratory. This device, an innovative administration and closure system for vials, is reusable and offers an optimal administration for products selected by Virbac.

The first deliveries are expected between the 1st and 2nd quarter of 2018. BIOCORP will then be responsible for the production of the industrialized product.

"We are thrilled to announce the signature of this industrialization contract with Virbac, which successfully concludes the R&D program custom-developed by our teams. This collaboration with Virbac, an expert in animal health, highlights the width of our scope and the wide range of applications of our expertise," commented Jacques Gardette, founder and CEO, and Eric Dessertenne, chief operating officer of BIOCORP.

Founded in 2004 in Issoire (near Clermont-Ferrand), France, BIOCORP is a French company specializing in the development and manufacturing of medical devices and innovative drug delivery systems. It is listed as an "innovative company" by the French public investment bank Bpifrance. With over 20 years of experience and more than 30 manufactured products, BIOCORP is a key player in the industry, providing drug delivery solutions that meet the evolving needs of patients. Today, BIOCORP continues to innovate in the area of medical plastics, its core business, and to market traditional devices (alternative to aluminum capsules, syringe, and vial administration systems) that have been an important source of recurring income. Its solid expertise and capacity to innovate have allowed the company to develop new internet-connected products, including the DataPen, a reusable smart injection pen that automatically transmits data to a mobile app, helping patients to manage their treatment; and treatment management add-ons, which adapt to existing delivery devices and are compatible with most injection pens in the market. The company has a team of 48 employees. For more information, please visit [www.biocorp.fr](http://www.biocorp.fr).

Founded in 1968 by a French veterinary doctor, Virbac is an independent pharmaceutical laboratory that has always been dedicated to animal health. Today ranked as the 7th veterinary company worldwide, the group has a global presence in over 100 countries and offers a comprehensive and practical range of products and services covering the majority of animal species and diseases. Linking the needs of health care providers to the latest technological advances, Virbac's innovation is supported by an industrial tool meeting the highest international quality standards. Virbac has been forging personalized relationships with veterinarians and farmers in each country for nearly 50 years. Through this privileged partnership, in which social, health, and environmental issues come together, Virbac contributes day after day to shape the future of animal health. For more information, please visit [www.virbac.com](http://www.virbac.com).

#### **Liquidia Technologies Announces Positive Phase 1 Data for LIQ865, Sustained-Delivery PRINT® Formulation of Bupivacaine for Postsurgical Pain Relief**

Business Wire: May 24, 2017 – RESEARCH TRIANGLE PARK, NC, U.S.A. – Liquidia Technologies, Inc., today announced initial data from its LIQ865 internal clinical development program, which is a PRINT® formulation for the sustained-delivery of free base bupivacaine for postsurgical pain relief. The phase 1 trial, marking the first evaluation of LIQ865 in humans, was a randomized, controlled, double-blind study evaluating the safety, pharmacokinetic profile, and pharmacodynamic response of a single-ascending dose in healthy adult males. Topline data indicate that LIQ865 doses were well tolerated, and the pharmacodynamic response was consistent with a local anesthetic effect lasting for three or more days.

"According to the National Institute on Drug Abuse, a component of the National Institutes of Health, 2.1 million people in the United States suffer from substance use disorders related to prescription opioid pain relievers, many of whom began taking opioids as postsurgical patients," said Mike Royal, M.D., LIQ865 program leader and senior vice president, clinical development at Liquidia. "Our intent with LIQ865 is to increase the options for long-lasting, safe, effective post-operative pain relief that can reduce the need for opioids in the early days following surgery."

Liquidia is developing LIQ865 with the goal of providing at least three days of post-surgical pain relief with a single administration, potentially minimizing or avoiding the need for opioid analgesics. There are over 80 million inpatient and outpatient surgeries performed every year, with the majority of surgeries requiring opioids to treat moderate to severe postoperative pain. A minority of these individuals will become long-term users and have the potential for opioid misuse and addiction.

“The phase 1 clinical trial results for LIQ865 further validate the remarkably broad applicability of the PRINT technology across virtually any therapeutic area,” said Neal Fowler, chief executive officer at Liquidia. “We look forward to providing additional updates on our PRINT technology-enabled clinical programs throughout 2017.”

Liquidia Technologies is a biopharmaceutical company that has pioneered a simple, elegant solution to improve the performance of medicines by precisely engineering drug particles. Through its proprietary PRINT technology, Liquidia has become the only company in the world that can improve the efficacy, safety, or route of administration, of nearly any therapeutic molecule by designing drug particles in a virtually unlimited number of compositions, sizes, or shapes. Combining aspects of biology and medicinal chemistry with polymer science, PRINT technology represents an entirely novel approach to drug development and production, yet one that is also GMP capable, fully scalable, and highly cost-effective. PRINT<sup>®</sup> technology-optimized product candidates are in clinical development in inhaled diseases, postoperative pain management, and ophthalmology. In addition to advancing product candidates from its own pipeline, Liquidia actively partners with world-class collaborators, including GlaxoSmithKline, to expand the applications for PRINT technology. Liquidia is based in Research Triangle Park, North Carolina. More information is available at [www.liquidia.com](http://www.liquidia.com).

### **Lysogene Selects Brammer Bio to Produce GM1 Gangliosidosis Gene Therapy Product**

Business Wire: May 24, 2017 – PARIS, France, and CAMBRIDGE, MA, U.S.A. – Lysogene (Paris: LYS) (FR0013233475 – LYS), a leading, biopharmaceutical company pioneering gene therapy technologies to treat central nervous system diseases, today announced that it has entered into a strategic manufacturing agreement with Brammer Bio, a best-in-class viral gene and cell therapy manufacturer.

Brammer Bio will produce LYS-GM101, an AAVrh10-based gene therapy, for clinical testing of the therapeutic candidate in patients with GM1 gangliosidosis, a rare neuronopathic lysosomal storage disorder.

“We are pleased to have secured Brammer Bio, a leading manufacturer with proven expertise in the development of robust industrial-scale manufacturing of AAV-based products, to provide the highest quality LYS-GM101 product for clinical testing,” said Mark Plavsic, chief technical officer at Lysogene. “This agreement ensures Lysogene has established commercial-ready gene therapy manufacturing in line with our need for the product.”

Preclinical data in animal models of GM1 show that LYS-GM101 treatment delivers a functional gene encoding the  $\beta$ gal enzyme resulting in a reduction of GM1 gangliosides and transforms the animal phenotype. These studies will support an Investigational New Drug application and the launch of the phase I clinical trial, expected to launch in 2019.

“We are delighted to partner with Lysogene to manufacture this commercial-ready AAVrh10 gene therapy product,” stated, Mark Bamforth, president and CEO of Brammer Bio. “We embrace this opportunity to help patients in need and re-affirm Brammer Bio’s leadership position as the manufacturer of choice in the gene therapy space.”

GM1 is an extremely severe, autosomal recessive disease caused by a mutation in the GLB1 gene encoding for the lysosomal acid beta-galactosidase ( $\beta$ gal) enzyme. The resulting enzymatic deficiency leads to accumulation of GM1-ganglioside in cells. Clinical presentation is mainly neurological with rapidly progressive impairment (motor, cognitive, and behavioral) leading to premature death, mostly in early childhood. It is a devastating disease for patients and families. There is currently no disease modifying treatment available.

Brammer Bio provides clinical and commercial supply of vectors for *in vivo* gene therapy and *ex vivo* modified-cell based therapy, along with process and analytical development, and regulatory support, enabling large pharma and biotech clients to accelerate the delivery of novel medicines to improve patients’ health. Brammer is owned by Ampersand Capital Partners, the only institutional investor in the company, and its founders. For more information, please visit [www.brammerbio.com](http://www.brammerbio.com).

Lysogene is a clinical-stage biotechnology company pioneering the basic research and clinical development of AAV gene therapy for CNS disorders with a high unmet medical need. Since 2009, Lysogene has established a solid platform and network, with lead products in mucopolysaccharidosis type IIIA and GM1 gangliosidosis, to become a global leader in orphan CNS diseases. Lysogene is listed on the Euronext regulated market in Paris (ISIN code: FR0013233475). For more information, visit [www.lysogene.com](http://www.lysogene.com).

### **Nemaura Pharma Memspatch Addresses Diabetics Fear of Needle Puncture Pain**

Business Wire: May 18, 2017 – LOUGHBOROUGH, England – Results of recent clinical trials carried out on type 1 diabetics by Nemaura Pharma using its Memspatch insulin micro-needle device (IMD) will come as a relief to those who fear needles and injections, a condition medically known as trypanophobia, affecting 10 percent of the world’s population.

Nemaura's Memspatch IMD compared favorably against a commonly use marketed pen injector (PI). The single-site clinical study involving 18 type 1 diabetic patients took place over two periods, with a pain assessment performed on each visit to evaluate the severity of the pain. The Numeric Pain Rating Score system 0–10 was used, which scores no pain at 0, through to 10 indicating the most intense pain sensation imaginable. Patients were asked to record their experience of the respective IMD and PI devices and to think about the intensity, sharpness, and itchiness of the pain immediately after administration.

While pain intensity and sharpness inflicted by the PI reached 5 for several patients, the Memspatch IMD recorded 0 or 1 when applied to the arm or thigh.

These major reductions in pain levels are a result of the novel approach Nemaura has taken to drug delivery systems. The Memspatch IMD is held flat against the skin, with skin-penetration confined to a depth of 2 mm to 4 mm, which is less than half the usual 9 mm depth for pen injector needles. Insulin delivery through shallow micro-needles requires little training or basic skills, making self-medication much easier.

Commenting on the study results, Nemaura CEO Dr. Faz Chowdhury said: "Needle phobia is a major barrier to health. We have looked carefully at the human factors restricting diabetics wanting to self-administer insulin, and have developed the Memspatch IMD to avoid puncture pain and to improve treatment compliance. Over 50% of adults with type 2 diabetes delay starting insulin due to needle fear, and over 90% feel fear reactions every time they inject. So we would encourage the take-up of Memspatch IMD technology to help diabetics better manage their condition."

Further Memspatch tests are planned later this year on a broad range of other medicines alongside insulin, as Nemaura moves toward commercial partner agreements on multiple medical conditions.

Founded in 2005, Nemaura Pharma is a private specialist biotech company with headquarters and research facilities in the Advanced Technology Centre on the Loughborough University Science and Enterprise Park (LUSEP) in the United Kingdom. Nemaura has patents secured or pending across multiple patent families and now employs over 25 medical device technologists and bio scientists based on the Loughborough University Science and Enterprise Park.

The company has secured over £25m (over \$30m) in licensing and development payments, and private investment. In addition, Nemaura has been awarded five highly competitive British Government grants, and the Frost & Sullivan 2016 Enabling Technology Leadership Award in Transdermal Drug Delivery.

#### **Elixir Medical Corporation Announces Outstanding 5-Year Clinical Data for CE Mark-Approved DESolve® Novolimus Eluting Bioresorbable Coronary Scaffold System**

Business Wire: May 17, 2017 – MILPITAS, 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 5-year clinical data from the DESolve Nx international pivotal clinical trial for the CE Mark-approved, fully bioresorbable DESolve® novolimus eluting coronary scaffold system. Stefan Verheye, M.D., Ph.D., ZNA Middleheim Hospital, Antwerp, Belgium, and co-principal investigator of the DESolve Nx trial, presented these long-term clinical and imaging results to a packed audience of the international cardiology community gathered at EuroPCR, the annual meeting of the European Association for Percutaneous Cardiovascular Interventions, in Paris, France.

The DESolve Nx clinical trial demonstrated that at the five-year end point, long after the full bioresorption of the DESolve scaffold, DESolve continues to show a low overall MACE rate (9.0%) with no additional CI-TLRs (clinically indicated target lesion revascularizations) from years 2 through 5, and no definite scaffold thrombosis through 5 years.

The DESolve scaffold achieves early degradation in 6 months and near complete resorption of the scaffold mass in one year. The DESolve Nx clinical trial confirmed complete resorption of the scaffold using OCT at the 36-month angiographic follow up. The mean lumen area measured by IVUS imaging at 6 months was maintained through 36 months demonstrating sustained efficacy of treatment with the DESolve scaffold.

"Elixir's DESolve is the only BRS (bioresorbable scaffold) to accomplish early degradation and resorption of the scaffold while maintaining excellent and sustained effectiveness, as evidenced by angiography and IVUS at 6, 18, and 36 month follow ups. In addition, the DESolve scaffold demonstrated excellent long term clinical safety without any concerns for the patients," said Dr. Verheye. "The continued low MACE rate with no late or very late scaffold thrombosis through 5 years, long after the scaffold is completely resorbed, clearly differentiates DESolve and demonstrates that not all BRSs are the same."

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“Early degradation and early resorption are not only intuitively desirable, they are imperative for BRS technology to succeed and eliminate late scaffold events. Other technologies have had challenges of structural integrity and chronic recoil with their fast-degrading scaffolds, and reverted to much longer degradation and resorption profiles in order to solve those issues. However, long resorption profiles can potentially result in late and very late safety clinical events affecting patient outcomes,” explained Motasim Sirhan, chief executive officer of Elixir Medical. “Elixir’s DESolve stands out as the only technology to have elegantly solved this contradiction of providing early degradation and resorption while achieving excellent clinical efficacy and safety as demonstrated by the DESolve Nx trial data.”

The 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  $0.20 \pm 0.32$  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 show lumen area increase at six months demonstrating vascular restoration; (b) degrade in six months and near complete resorption in one year with the intent to eliminate late and very 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 over-expansion.

Elixir Medical also announced excellent six-month primary endpoint safety and efficacy data of the DESolve Cx Clinical Study at EuroPCR. Prof. Alexandre Abizaïd, M.D., Ph.D., of the Instituto Dante Pazzanese de Cardiologia, Brazil, and co-principal investigator of the DESolve Cx Trial, presented the clinical and imaging results to a packed audience of the international cardiology community gathered in Paris for the annual meeting of the European Association for Percutaneous Cardiovascular Interventions. The DESolve Cx Novolimus Eluting Bioresorbable Coronary Scaffold leverages the proven DESolve technology, has a strut thickness of 120  $\mu$ m, and degrades in six months with near complete resorption in 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, Elixir’s DESolve Cx demonstrated excellent late lumen loss of  $0.19 \pm 0.25$  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% and an increase in scaffold and lumen area between baseline and six months, confirming early uncaging of the vessel. Excellent acute scaffold strut apposition and embedding was observed with intravascular optical coherence tomography (OCT) imaging. A demonstration of vasomotion (response of the blood vessel to stimulus) of the scaffolded vessel utilizing nitroglycerin infusion was also accomplished at 6-month follow-up.

The DESolve Cx clinical trial is a 50-patient, single-arm, multi-center evaluation of the Elixir’s next-generation, thin-strut DESolve Cx novolimus-eluting bioresorbable coronary scaffold system. The patients were enrolled in Europe and Brazil and will continue to be followed up through two years.

“The outstanding clinical trial results of the DESolve Cx with excellent safety and performance data position this product as a workhorse, next-generation bioresorbable scaffold system for clinicians seeking to improve clinical outcomes in a broad patient population,” said Dr. Abizaïd. “Since the Cx utilizes DESolve’s proven technology for long-term safety and efficacy, it is poised to be competitive with the best-in-class drug eluting stent systems, bringing the added advantage of being completely resorbed in the body and return the vessels to a *de novo* state.”

“The 6-month results for the DESolve Cx clinical trial patients reinforce Elixir’s commitment of providing cardiologists with more deliverable and user-friendly coronary scaffolds for their 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 safe and effective fully resorbable coronary scaffolds to help physicians confidently treat the patient’s blocked coronary arteries and return them to their *de novo* state.”

The fully bioresorbable DESolve™ 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) show lumen area increase at six months demonstrating vascular restoration; (b) degrade in six months and near completely resorb in one year with the intent to eliminate late and very 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 over-expansion.

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Elixir Medical Corporation, a privately held company headquartered in Milpitas, California, develops products that combine state-of-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](http://www.elixirmedical.com).

### **Svelte Medical Systems Announces Sustained Outstanding Outcomes in Clinical Studies**

Business Wire: May 16, 2017 – PARIS, France – Final 5-year outcomes from the DIRECT first-in-man study were presented at the EuroPCR symposium today, with 0% clinically driven target lesion revascularization (TLR), target vessel failure (TVF), and major adverse cardiac events (MACE) reported. The DIRECT single-arm study enrolled 30 patients at four centers in New Zealand to assess the feasibility of the Svelte drug-eluting coronary stent-on-a-wire integrated delivery system (IDS) in patients undergoing percutaneous coronary intervention.

“Longer-term follow-up of novel coronary stents is very important, as shown by the recent findings of unexpectedly high rates of very late thrombosis in bioresorbable scaffolds. The absence of late adverse clinical events through 5 years is unusual in any stent study. Considering half of the lesions treated in DIRECT were type B2/C and 97% device success was achieved despite all investigators being first-time operators with the system, I am very impressed with these results,” said Mark Webster, interventional cardiologist at Auckland City Hospital and principal investigator of the DIRECT study.

Positive outcomes were also reported in the DIRECT II study through 3 years. In patients treated with the Svelte IDS, 3-year MACE remained unchanged from 1 year at 3.7%, while in the control arm, MACE increased from 7.8 to 9.8%. Neither arm had reports of stent thrombosis through 3 years.

DIRECT II is a prospective, randomized, multi-center clinical study comparing the safety and efficacy of the Svelte IDS with the Medtronic Resolute Integrity™ drug-eluting coronary stent in 159 patients. Direct stenting was performed in approximately 90% of lesions. Though powered only to demonstrate non-inferiority in 6-month angiographic outcomes between both arms, the DIRECT II study continues to demonstrate numerical superiority of the Svelte IDS arm compared with the control arm in all clinical outcomes through 3 years. The Svelte arm further exhibited reduced procedure and device times, with trends toward reduced fluoroscopy time and contrast use compared with the control arm, confirming results observed in prior studies utilizing the Svelte IDS.

“The long-term results observed in the DIRECT and DIRECT II studies, coupled with no reports of stent thrombosis now through 5 years, indicate our technologies provide excellent and sustained patient outcomes,” said Jack Darby, president and CEO of Svelte Medical Systems. “Our unique approach to stent delivery and bio-friendly drug coating allow physicians to streamline PCI and achieve best-in-class results, delivering both clinical and economic value to the healthcare system. We look forward to serving more patients and physicians around the globe.”

Svelte is working with the FDA and PMDA to obtain regulatory approvals for clinical evaluations of its DES technologies in the United States and Japan and plans to initiate a clinical study during the second half of 2017. The IDS, incorporating Asahi ACT ONE™ wire technology and a proprietary low-compliant delivery balloon, is commercially available in select accounts in Europe as SLENDER IDS. Svelte has additionally developed a rapid-exchange system (DIRECT RX) using the same proprietary DES and balloon technologies, which attained CE Mark certification last year.

Headquartered in New Providence, New Jersey, Svelte Medical Systems ([www.sveltemedical.com](http://www.sveltemedical.com)) is a privately held company engaged in the development of highly deliverable balloon expandable stents. Statements made in this press release that look forward in time or that express beliefs, expectations, or hopes regarding future occurrences or anticipated outcomes or benefits are forward-looking statements. A number of risks and uncertainties, such as risks associated with product development and commercialization efforts, results of clinical trials, ultimate clinical outcomes and benefit of the company's products to patients, market and physician acceptance of the products, intellectual property protection, and competitive product offerings, could cause actual events to adversely differ from the expectations indicated in these forward-looking statements.

### **Micell Technologies Announces MiStent Achieved Primary Endpoint in All-Comers Randomized Clinical Trial Versus Xience**

PRNewswire: May 16, 2017 – PARIS, France – Micell Technologies announced today at the late-breaking trial session of EuroPCR—the official congress of the European Association of Percutaneous Cardiovascular Interventions—positive 12 month data from its DESSOLVE III clinical trial. The study met its primary endpoint, showing non-inferior safety and effectiveness outcomes in a complex patient population for the MiStent® sirolimus-eluting absorbable polymer coronary stent system (MiStent) versus the Xience®

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everolimus-eluting coronary stent system (Xience). Prof. Robbert J. de Winter, M.D., Ph.D., Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands, presented the data.

Prof. de Winter commented, “MiStent met the primary non-inferiority endpoint of target lesion failure (TLF) at 12 months, with numerically lower TLF and target lesion revascularization (TLR) rates. TLR rates for MiStent were numerically lower at all time points following the procedure, and by one year that difference grew to 1.2%. These results speak to the potential value of slower, controlled drug release allowing for sustained drug presence. These trial results, in conjunction with the five-year results from the DESSOLVE I and II studies, provide further evidence of the potential value of this technology relative to current DES performance expectations from the perspectives of both safety and efficacy.”

DESSOLVE III is a prospective, balanced, randomized, controlled, single-blind, multi-center all-comers study comprising 1,400 patients. Enrollment was completed in December 2015, and this presentation highlighted 12 month primary endpoint outcomes. The study is being conducted independently by the European Cardiovascular Research Institute, Rotterdam, The Netherlands, and is supported by Micell Technologies. The study design and conduct were overseen by a steering committee including Profs. Patrick Serruys, Robbert de Winter, and William Wijns.

Patients in this trial suffered from symptomatic coronary artery disease, including those with chronic stable angina, silent ischemia, or acute coronary syndrome (including non-ST-elevation myocardial infarction and ST-elevation myocardial infarction) and qualified for percutaneous coronary interventions. The primary endpoint for this trial was a non-inferiority comparison of TLF for the MiStent group versus the Xience group at 12 months postprocedure.

Dennis Donohoe, M.D., Micell's chief medical advisor, said, “These results appear to validate the unique premise of Micell's supercritical fluid technology platform, which allows drug in micro-crystalline form to be combined with a fast-dissolving polymer and applied as a coating on an ultra-thin-strut cobalt chromium stent. These unique features have the potential to offer meaningful clinical and economic benefits to patients and the healthcare system.”

In a session on novel drug-eluting stent technologies, Prof. Krzysztof Milewski, lead investigator for the DESSOLVE III OCT sub-study, highlighted positive outcomes from assessments of optical coherence tomography (OCT) images from MiStent and Xience patients at 6 months. Neointimal hyperplasia volume obstruction was statistically lower for MiStent ( $15.0 \pm 4.1\%$  versus  $18.9 \pm 6.2\%$ ;  $p < 0.01$ ). Similarly, both abluminal neointimal hyperplasia volume and area were significantly better with MiStent by  $13.3 \text{ mm}^3$  ( $p = 0.02$ ) and  $0.33 \text{ mm}^2$  ( $p < 0.01$ ), respectively. Both groups demonstrated equal and almost complete strut coverage. “We observed a statistically significant difference in favor of MiStent,” confirmed Prof. Milewski, M.D., Ph.D., general director, Center for Research and Development for the American Heart of Poland S.A. “These OCT data further demonstrate that the unique pharmacokinetics of MiStent, with its micro-crystalline sirolimus, reduce the factors that lead to late lumen loss requiring vessel revascularization.”

Additional data and an overview of the rationale and design of the OCT assessments presented by Prof. Milewski will be the subject of a late-breaking trial submission, also at EuroPCR, on May 18. Prof. Milewski will present “OCT and IVUS Imaging for Evaluation of Stent-Based Therapies: DESSOLVE III, a Randomised OCT Sub-Study Comparison of Xience vs MiStent.”

MiStent is designed to optimize clinical performance and healing in patients with coronary artery disease. The rapidly absorbable coating of MiStent, which contains micro-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. MiStent has received CE marking but is not approved for sale in the United States.

### **Cingulate Therapeutics Initiates First Human Clinical Trial**

PRNewswire: May 13, 2017 – KANSAS CITY, KS, U.S.A. – Cingulate Therapeutics, LLC, a privately held biopharmaceutical company focused on the development of new and innovative products for the treatment of attention deficit/hyperactivity disorder (ADHD), is proud to announce its transition to a clinical stage development company with the initiation of dosing in its proof of concept trial for CTX-1301, one of two proprietary, first-line stimulant medications the company is developing for the treatment of ADHD. The four-week human clinical trial of CTX-1301 is being conducted in Glasgow, Scotland, by its development partner Bio-Images Drug Delivery (BDD Pharma).

The randomized, three arm, open-label crossover study is being conducted in healthy volunteers to establish the *in vivo* pharmacokinetic behavior of CTX-1301 using both gamma scintigraphic imaging and traditional assays to evaluate the body's absorption, distribution, metabolism, and excretion of CTX-1301. CTX-1301, like its co-lead product CTX-1302, has a target product profile designed to deliver a rapid onset, last the entire active day, and minimize the afternoon crash with minimal impact on sleep and appetite. Both assets utilize proprietary, multi-core timed-release OralogiK™ technology developed by CTx's partner BDD. Multiple, positive *in vitro* data sets have demonstrated the desired triphasic controlled-release functionality. The company anticipates reporting findings from this trial in the third quarter of 2017.

Shane J. Schaffer, PharmD, chairman and chief executive officer of Cingulate Therapeutics, said, "The breakthrough multi-core technology employed in CTX-1301 and CTX-1302 combines layers of immediate, delayed, and sustained release medication in a single tablet intended to deliver the appropriate dose and at the right time when ADHD patients need it. This study intends to demonstrate the ability of our technology to achieve the target product profiles in advance of filing separate IND applications with the U.S. Food and Drug Administration by the end of this year."

Both assets utilize the innovative, proprietary timed-release technology OralogiK developed by CTx's partner BDD. Dr. Carol Thomson, CEO of BDD, said, "We are delighted to be working with Cingulate Therapeutics to develop this exciting new product which is now undergoing clinical evaluation using our pharmaco-scintigraphic capabilities. The OralogiK technology is uniquely positioned to deliver the triphasic release profile required of the CTX-1301 and CTX-1302 products."

Cingulate Therapeutics, LLC, is a privately held clinical-stage biopharmaceutical company focused on the development of new and innovative products for the treatment of attention deficit/hyperactivity disorder (ADHD). Cingulate is developing two proprietary, first-line medications, CTX-1301 and CTX-1302, for the treatment of ADHD intended for all patient segments: children, adolescents, and adults. CTX-1301 and CTX-1302 utilize an innovative, flexible core tableting technology with a target product profile designed to deliver a rapid onset, last the entire active day, and minimize the afternoon crash with minimal impact on sleep and appetite. The company has initiated proof of concept phase I clinical trials and plans to implement the full clinical plan for both CTX-1301 and CTX-1302 in early 2018. Cingulate anticipates filing INDs for CTX-1301 and CTX-1302 via the accelerated 505 (b) (2) regulatory pathway. The company has offices in Kansas City, Kansas, and Morristown, New Jersey. For more information, visit [www.cingulatetherapeutics.com](http://www.cingulatetherapeutics.com).

Bio-images Drug Delivery Ltd. (BDD) is a privately owned drug delivery company specializing in the development of modified and controlled release oral formulations. BDD's OralogiK™ technology is a tablet-in-tablet drug delivery system providing timed release, sustained release, and the opportunity for complex bi- and triphasic release of one or multiple drugs. The OralogiK™ technology is protected with granted patents in the United States, European Union, and Japan. BDD has in-house clinical trial capabilities for conduct of gamma scintigraphic/pharmacokinetic studies in men. For more information, visit [www.bddpharma.com](http://www.bddpharma.com). ■