

### What's Inside

Alkaline Protease Enzyme as a Biological Skin Permeation Enhancer: Breaking Down the Barrier

Modular Assembly of Immune Signals into Polyelectrolyte Multilayers to Promote Immunological Tolerance

**CRS** Annual Meeting

DDTR Update

**Chapter News** 



**Controlled Release Society Annual Meeting & Exposition** 

**BOSTON** July 16–19, 2017

### **COLLABORATE** CONNECT **INNOVATE**

# **Speakers to Ignite Your Imagination**



**Henry Brem** John Hopkins University



Paula T. Hammond Massachusetts Institute of Technology



**Robert S. Langer** Massachusetts Institute of Technology



**Amar Sawhney** Ocular Therapeutix, Inc.



### **#CRSboston**



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Ryan Donnelly Editor



Steven Giannos Editor



Medha Joshi Editor



Arlene McDowell Editor



Bozena Michniak-Kohn Editor



Rod Walker Editor



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### > TABLE OF CONTENTS

- 4 From the Editor
- 5 Letter from CRS President Ruth Schmid
- 6 2017 Controlled Release Society Annual Meeting & Exposition
- **9** Scientifically Speaking Alkaline Protease Enzyme as a Biological Skin Permeation Enhancer: Breaking Down the Barrier
- **12** Scientifically Speaking Modular Assembly of Immune Signals into Polyelectrolyte Multilayers to Promote Immunological Tolerance
- **17** DDTR Update Drug Delivery and Translational Research Update
- **18** Chapter News CRS Nordic Chapter Meeting
- 21 Chapter News Drug Delivery Australia 2016
- 22 Chapter News Pharmaceutical Innovations: Academia Meets Industry
- 25 People in the News
- 26 Companies in the News

Cover image: 3D render of nerve cells by Ralwel / Shutterstock.com

### > FROM THE EDITOR

#### Editors

Ryan Donnelly Steven Giannos Medha Joshi Arlene McDowell Bozena Michniak-Kohn Rod Walker

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

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

Telephone: +1.651.454.7250 Facsimile: +1.651.454.0766

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

Contact Brianna Plank; telephone +1.651.994.3819, or e-mail at bplank@ scisoc.org for information about exhibiting, advertising, or other visibility opportunities. Roderick B. Walker Rhodes University South Africa



### **Times Are Changing**

As you all sit down to read this issue of the CRS Newsletter to get a dose of excellent controlled release science it is opportune to reflect on the world as we know it and the potential impact of some recent decisions. Ruth Schmid, the CRS President, has penned a statement in respect of the recent executive order from the White House regarding immigration into the United States. The stance of the CRS leadership is admirable in this respect, as is that of the CEO of the American Association for the Advancement of Science, in which there is a plea for transparency and exchange of ideas. Indeed, this is much needed sanity in a changing world. It is perhaps even more fitting to note that there have been two attempts to promote isolation from the newly elected President of the United States and both have failed from a legal perspective. This issue is not new, but it has been made explicit by the order. I recall at the Chicago meeting a colleague from Europe bemoaning the fact that one of his students who happened to be from the Middle East had been held at immigration for a number of hours and yet another requesting at the general meeting the leadership take cognisance of this issue. Once again I implore CRS leadership to endeavour to ensure that CRS and its offerings on whichever continent are accessible to all interested scientists.

Notwithstanding the current failure of President Trump to ban entry into the United States to citizens of some countries, I am very concerned as to the ultimate outcome of this folly and believe that as scientists we should—no, *must*—stand against such notions of exclusion, as diversity of opinion, skill, thinking, ability, and sharing is vital to understand the multiple needs of society and to find lasting solutions to the health and other challenges that face the global population.

Bob Dylan hit the nail on the head in his song "The Times They Are a-Changin'," and the words are as poignant now as when they were first penned. We need to be vigilant and cannot allow strength in diversity to be diluted by thoughtless decision making, and I hope that sanity will prevail in the near future to allow persons of all nations to work closely together, as most individuals are, in general, for the greater good of all.

Enjoy the read, learn some updated science, and reflect on what could be if we were all able to lend a hand to resolve health challenges together without being marginalised due to our religion, country of origin, or other consideration beyond our control.



CRS Statement Regarding U.S. White House Immigration Policies

Dear CRS Members,

The White House has recently issued an Executive Order that places restrictions on travel to the U.S. for citizens of several countries.

CRS leadership is troubled by this policy on many levels, including the negative impact it will have on the ability of scientists to participate in the exchange of ideas that are vital to the advancement of science, including our field. CRS takes great pride in its culture of diversity and global reach. This diversity and our attitude of inclusion greatly strengthens our society.

While this order is deeply troubling, we note that it is currently scheduled to expire in 90 days, so it might not restrict attendance of the Boston meeting in July by our valued members in the affected countries. CRS is your professional society and a global home for your science. We recognize that diversity makes science stronger and collaboration across the globe is imperative for advancing our field.

Thank you,

Ruth Schmid President, Controlled Release Society

### Four Remarkable Plenaries at the CRS Annual Meeting

Come to the CRS Annual Meeting to be inspired by the best and brightest in delivery science. Four stellar plenary speakers will be a highlight of the event, with Robert Langer opening the conference. Plan now to join us July 16–19 in Boston, Massachusetts, U.S.A.

### Sunday, July 16 •



Robert S. Langer Massachusetts Institute of Technology, U.S.A.

### Controlled Drug Delivery Systems and the Creation of New Medical Treatments

Advanced drug delivery systems are having an enormous impact on human health. The presentation will start by discussing Langer Lab's early research on developing the first controlled release systems for macromolecules and the isolation of angiogenesis inhibitors (enabled by using these delivery systems) and how these led to numerous new therapies. This early research then led to new drug delivery technologies, including nanoparticles and nanotechnology, that are now being studied for use in treating cancer and other illnesses and for use in vaccine delivery. We will then discuss ways of developing novel microchips for drug delivery and developing new super-long acting oral delivery systems that can deliver drugs to combat diseases in the developing world. Approaches for synthesizing new biomaterials, such as biodegradable polyanhydrides, will be examined, and examples where such materials are used in brain cancer and other diseases will be discussed. Finally, by delivering mammalian cells, including stem cells, with synthetic polymers, new approaches for engineering tissues are being developed that may someday help in various diseases. Examples in the areas of cartilage, skin, blood vessels, and spinal cord repair will be discussed.

**Robert Langer** is the David H. Koch Institute Professor at MIT (there are 13 Institute Professors at MIT; being an Institute Professor is the highest honor that can be awarded to a faculty member). He has written more than 1,350 articles and has over 1,130 issued and pending patents worldwide.

His many awards include the U.S. National Medal of Science, the U.S. National Medal of Technology and Innovation, the Charles Stark Draper Prize (considered the engineering Nobel Prize), the Albany Medical Center Prize (largest U.S. medical prize), the Wolf Prize for Chemistry, the 2014 Kyoto Prize, and the Lemelson-MIT prize, for being "one of history's most prolific inventors in medicine." Langer is one of the very few individuals ever elected to the National Academy of Medicine, the National Academy of Engineering, and the National Academy of Sciences.

#### Monday, July 17 -



Henry Brem Johns Hopkins University, U.S.A.

### The Changing Role of Drug Delivery in Brain Tumor Therapy

Local delivery is being utilized to target multiple pathways to improve therapeutic options for brain tumor therapy. Through the combination of Gliadel, radiation therapy, and oral temozolomide (TMZ), median patient survival has increased from 9 to 21 months. We are exploring the synergy of combining locally delivered therapeutic compounds. We are exploring the efficacy of locally delivered acriflavine, an antiseptic and antifungal agent, which significantly prolongs survival in rodent glioma models. We are using ultrasound to increase the distribution of pectin-based nanoparticles and to enhance the permeability of the cell membrane to allow for increased therapeutic efficacy. A logical evolution of local controlled release is the creation of devices that release multiple agents in multiphasic patterns to optimize therapeutic regimens or more accurately recapitulate the physiologic norm. This was addressed with the development of biodegradable poly(L-lactic acid) multi-well passive microchips with poly(D,L-lactic-*co*-glycolic acid) membranes.

continued

### CRS Annual Meeting & Exposition continued

Development of this therapy heralds a new approach to brain therapeutic research, offering the ability to circumvent physiologic barriers and effectively deliver a multitude of novel agents. The immunosuppressive effects of chemotherapy present a challenge for effectively combining chemotherapeutic agents with immunotherapy. The combination of local chemotherapy and targeted antibodies to the programmed cell death protein 1 (anti-PD-1) shows a strong survival and immunologic benefit in glioma-bearing mice compared with mice receiving systemic chemotherapy and anti-PD-1. This study provides proof of principle for superior efficacy of local chemotherapy delivery in combination with immunotherapy for primary brain tumors. Through the combination of these approaches we are hoping to deliver more potent biological agents to continue to improve the survival and quality of life for cancer patients.

**Henry Brem** is the Harvey Cushing Professor of Neurosurgery at The Johns Hopkins University, director of the Department of Neurosurgery and neurosurgeon-in-chief of The Johns Hopkins Hospital. He also is a professor of oncology, ophthalmology, and biomedical engineering. Over the past 30 years, Dr. Brem has introduced new therapeutic approaches to neurosurgery. His dedication to patient care, clinical excellence, teaching, and translational science has brought together a unique group of neurosurgeons and investigators who are changing the field of neurosurgery.

Tuesday, July 18 =



Amar Sawhney Ocular Therapeutix, Inc., U.S.A.

### Crosslinked PEG Hydrogels: A Versatile Family of Biomaterials and Their Application in Ocular Drug Delivery

PEG-based macromers that can be further polymerized to form cross-linked hydrogels now find numerous applications as surgical sealants, adhesion barriers, biopsy track and vascular puncture closure systems, abdominal aneurysm stent grafts, radiotherapy spacers, fiducial markers, and now drug delivery systems. The selection of the precursors that form these hydrogels in terms of their molecular weight, degree of branching, end functionalities, as well as built-in degradable segments allow for the creation of a vast family of biomaterials with widely varying physical and chemical properties. Yet these materials can be rapidly formed under gentle physiologically compatible conditions. New drugs relying on PEG hydrogels are at the brink of creating radical change of the way drugs are administered to the eye.

Amarpreet Sawhney has been President, CEO, and a member of the Ocular Therapeutix's board since cofounding the company in 2006 and Chairman of the Board since 2014. He served as CEO of Augmenix (2008–2014) and is a general partner of Incept, LLC. He was a founder of Confluent Surgical, Focal, Inc., and AccessClosure, Inc., prior to their acquisitions. Dr. Sawhney's innovations are the subject of over 100 issued and pending patents. He holds M.S. and Ph.D. degrees in chemical engineering from the University of Texas in Austin and a B.Tech. in chemical engineering from the Indian Institute of Technology, Delhi, India.

### Wednesday, July 19



**Paula Hammond** Massachusetts Institute of Technology, U.S.A.

### Nanolayers for Drug Delivery: From Cancer to Wound Healing

The alternating adsorption of oppositely charged molecular species, known as the electrostatic layer-by-layer (LBL) process, is a simple and elegant method of constructing highly tailored ultrathin polymer and composite thin films. We have utilized this method to develop thin films that can deliver proteins and biologic drugs such as growth factors with highly preserved activity from surfaces with sustained release periods of several days; manipulation of the film composition can lead to simultaneous or sequential release of different components, resulting in highly tunable multi-agent delivery (MAD) nanolayered release systems for cancer nanoparticle, tissue engineering, biomedical device, and wound healing applications.

continued

#### CRS Annual Meeting & Exposition continued

**Paula T. Hammond** is the David H. Koch Professor of Engineering and the department head of the Chemical Engineering Department at the Massachusetts Institute of Technology, as well as a member of MIT's Koch Institute for Integrative Cancer Research, her research in nanotechnology encompasses the development of new biomaterials to enable drug delivery from surfaces with spatial and temporal control. She investigates novel responsive polymers for targeted nanoparticle drug and gene delivery. Prof. Hammond was elected into the 2013 class of the American Academy of Arts and Sciences. She was one of the top 100 materials scientists named by Thomson Reuters and was named one of the World's Most Influential Scientific Minds in 2014.

For a complete listing of scientific sessions and invited speakers, visit controlledreleasesociety.org/meetings/annual/program/Pages/default.aspx.

### **CRS Annual Meeting Highlights**

### Women in Science Networking Event

Don't miss this popular event, which provides an insightful and informational presentation along with ample time for networking. This year's featured speaker is plenary speaker **Paula T. Hammond**, MIT, Department of Chemical Engineering.

### Research and Life Matters: Seeking Passion and Sanity in Career

Tuesday, July 18, 5:30 - 7:00 p.m.

Scientific and engineering careers provide some of the greatest outlets for creativity, discovery, and fulfillment. Although there are many challenges to seeking a career in a field that can be both inspiring and, at times, discouraging, there are also strategies and perspectives that can help provide grounding and leverage efforts toward success. Flexibility is essential in the ways in which we connect research, life, career, family, and other passions at different stages of life. These and any other issues regarding research or broader aspects of career will be discussed.

Additional registration, payment, and ticket required. Registration opens mid-March.

### Mini-Symposia

### Intracellular Delivery

Mauro Ferrari, Houston Methodist, U.S.A. Klavs Jensen, MIT, U.S.A.

The delivery of therapeutic agents directly to specific cellular organelles can dramatically increase therapeutic efficacy. In most cases, however, the distribution of therapeutics inside cells and to their intracellular targets remains a formidable challenge. The main barrier to intracellular delivery is the translocation of therapeutic molecules across the cell membrane, and ultimately through the membranes of their target intracellular organelles. Another prerequisite for efficient intracellular localization of active molecules is their escape from the endocytic pathway. Pharmaceutical nanocarriers can be engineered with both intracellular and organelle-specific targeting moieties to deliver encapsulated or conjugated cargo to specific subcellular targets. The advent of novel nanocarriers and targeting ligands as well as the exploration of alternate routes for intracellular delivery and targeting have prompted extensive research and promise an exciting future for this field.

### Natural Structures as Drug Carriers

Raymond Schiffelers, University Medical Center Utrecht, The Netherlands Mauro Magnani, Università degli Studi di Urbino Carlo Bo, Italy Andras Lacko, UNT Health Science Center, U.S.A.

Natural structures, such as cells, exosomes, and lipoproteins can transport a broad variety of substances in the body for effective delivery to their required locations. Due to their size, biocompatibility, and long time in the circulation, these natural structures are considered good candidates for drug delivery. Exosomes, natural and reconstituted lipoproteins, and certain cells are being actively evaluated as promising drug delivery vehicles and dosage forms. These structures have a good loading capacity, can be additionally modified to impart targetability and other useful properties, and are amenable to receptor-mediated uptake by target cells. The latest developments in this challenging and promising area will be discussed at this session.

### Alkaline Protease Enzyme as a Biological Skin Permeation Enhancer: Breaking Down the Barrier

Mohamed I. Nounou,<sup>a,b,c</sup> Nehal A. Ahmed,<sup>d</sup> Labiba K. El-Khordagui,<sup>b</sup> Amira Abouelfetouh Eid,<sup>e</sup> and Taha I. Zaghloul<sup>d</sup>

### Introduction

Microorganisms are contributing to a great degree nowadays in the field of biotechnology, with increasing demand as they provide a wide range of by-products that show promising economic importance and value in many specialized branches of biotechnology such as the food industry, leather industry, waste management, detergent industry, and medical and pharmaceutical applications.<sup>1,2</sup> Microbial enzymes offer substantial and increasingly important advantages over chemical catalysts in several ways: they are derived from renewable resources, are biodegradable, work under relatively mild conditions of temperature and pH, and tend to offer exquisite selectivity in both reactant and product stereochemistry.

Alkaline protease enzymes are produced from recombinant bacteria, in a high yield. The enzymes can be explored for various industrial and biomedical applications. The aim of the present work was to investigate the effect of keratinase enzyme, an alkaline protease, on the structural integrity of the skin to provide information necessary for various medical and pharmaceutical applications.

### **Experimental Methods**

*Ex Vivo* Skin Permeation Studies. Rhodamine B permeation across rabbit ear skin was assessed *in vitro* at  $32 \pm 0.5^{\circ}$ C using Franz diffusion cells. The skin samples were pretreated with the enzyme. This was followed by permeation of the dye for 2 and 24 h at  $32 \pm 0.5^{\circ}$ C. The effect of enzyme concentration in terms of enzyme units (5, 10, 20, 25, and 30 units) applied to the skin and enzyme pretreatment time (15, 30, 45, and 60 min) as experimental variables was investigated.

**Transepidermal Water Loss (TEWL) Measurements.** TEWL was determined *ex vivo* in a separate experiment as reported elsewhere.<sup>3</sup> Skin samples were mounted in vertical Franz diffusion cells (PermeGear, Bethlehem, PA, U.S.A.). The receiver phase was 12.2 mL of phosphate-buffered saline (PBS), pH 7.4, stirred at 400 rpm at 32 ± 0.5°C. TEWL was measured using an AF103 AquaFlux device (Biox Systems, London, U.K.) inserted into an empty donor cell secured over each skin sample.

**Transdermal Delivery of Vardenafil in a Rat Model.** The effect of enzyme pretreatment on the transdermal delivery of vardenafil as model drug applied in a 2% hydroxypropyl methyl cellulose (HPMC) gel vehicle was investigated using Sprague Dawley rats (120–140 g, n = 6). A 1 mL sample of PBS, pH 7.4, containing 20 units of alkaline protease was used to pretreat the marked skin application area for 30 min. Afterward, the enzyme was wiped off, and the application area was cleaned with distilled water. Post enzyme pretreatment, 500 µL of the 2% vardenafil gel was applied to the 3 cm<sup>2</sup> circular area.

**Histopathological Examination and Morphometric Measurements of Skin Samples.** This was conducted on both rabbit ear pinna skin samples used in the *ex vivo* permeation study and dorsal skin, posterior to the scapulae grafted out of the Sprague Dawley rats used in the *in vivo* permeation study after sacrificing the rats five days subsequent to the permeation study. Test and control skin samples were fixed in 10% formalin and stained with hematoxylin and eosin (H&E) and Masson's trichrome stains.

### **Results and Discussion**

Alkaline protease pretreatment of rabbit ear skin resulted in a significant increase in rhodamine B permeation, the effect being more pronounced at the longer permeation time (24 h). The fold increase in dye permeation reached its maximum at 20 enzyme units and 30 min pretreatment time (Fig. 1A and B). The *in vitro* skin permeation studies were confirmed via TEWL analysis (Fig. 1C and D, Table 1). Histopathological examination of enzyme-treated skin, along with TEWL data, indicated obvious proteolytic and keratinolytic effects of the enzyme that were dependent on enzyme activity (units) and pretreatment time (Fig. 2).

continued

<sup>&</sup>lt;sup>a</sup> Department of Pharmaceutical Sciences, Appalachian College of Pharmacy, Oakwood, VA 24631, U.S.A.

<sup>&</sup>lt;sup>b</sup> Department of Pharmaceutics, Faculty of Pharmacy, Alexandria University, Alexandria, 21521, Egypt.

<sup>&</sup>lt;sup>c</sup> Corresponding author. E-mail: nounou@acp.edu

<sup>&</sup>lt;sup>d</sup> Department of Biotechnology, Institute of Graduate Studies and Research (IGSR), Alexandria University, Alexandria, 21526, Egypt.

<sup>&</sup>lt;sup>e</sup> Department of Dermatology, Faculty of Medicine, Alexandria University, Alexandria, 21521, Egypt.

### Scientifically Speaking Nounou continued

Furthermore, treatment with the enzyme significantly enhanced the transdermal delivery of vardenafil, as indicated by the drug levels in the rats' plasma 30 and 60 min postapplication (Fig. 3).

### Conclusions

Data obtained on the effect of alkaline protease on skin structure and function indicated controllable enzyme-induced skin permeabilization. Transdermal drug delivery data provided a proof of concept for a new biological skin permeation enhancement approach with minimal skin damage. The study outcomes coupled with the economic aspects of enzyme production through recombinant bacteria offer great promise as a basis for diverse biomedical and pharmaceutical skin applications. These may include skin permeation enhancement in dermal and transdermal drug delivery, wound debridement, and treatment of



Figure 1. (A and B) Effect of pretreatment of rabbit ear skin with alkaline protease enzyme on the permeation of rhodamine B dye, where A illustrates effect of enzyme concentration (units/mL) and B shows the effect of enzyme pretreatment time. (C and D) Effect of pretreatment of rabbit ear skin with alkaline protease enzyme on transepidermal water loss (TEWL) flux (g/m<sup>2</sup>h), where C illustrates effect of enzyme concentration (units/mL) and D shows the effect of enzyme retreatment time.



Figure 2. (A) Hematoxylin and eosin (H&E) and Masson's trichrome (MT) stained male Sprague Dawley rat histological sections pretreated with 20 units of alkaline protease enzyme for 30 min versus untreated skin after post-in vivo treatment with 2% vardenafil hydroxypropyl methyl cellulose (HPMC) gel versus untreated skin. Animals were sacrificed five days posttreatment, and skin grafts were collected and stained (original magnifications ×100 and ×200). (B) Effect of in vivo pretreatment of male Sprague Dawley rat skin with alkaline protease enzyme (20 U/mL for 30 min) on the thickness of the epidermis and dermis of rats sacrificed five days posttreatment with 2% vardenafil HPMC gel, using H&E stains.

# Table 1. Correlation Between Transepidermal Water Loss and *Ex Vivo* Fold Increase in Permeation at 2 and 24 h Results as Represented by Probability (*P*) and Pearson (*r*) Correlation Coefficient Values

Time (h)	Effect of Pretreatment <i>P</i> Value	Time Pearson <i>r</i> Value	Effect of Enzyme P Value	Concentration Pearson <i>r</i> Value
2	0.184	0.816	0.019	0.981
24	0.136	0.864	0.078	0.922



Figure 3. Effect of pretreatment of the skin of male Sprague Dawley rats with alkaline protease enzyme (20 U/mL for 30 min) on the transdermal delivery of vardenafil applied as 2% hydroxypropyl methyl cellulose gel. Data expressed as vardenafil blood level 2 and 24 h postapplication.

hyperkeratinization skin conditions. Further investigations are encouraged to transform this promising biological tool, the keratinase proteolytic enzyme, from bench to bedside in pharmaceutical topical applications via optimized formulation parameters and tailored dosage form design. Finally, we believe that cheap, effective, reproducible, and easily scalable industrial biological products, represented by alkaline protease enzyme, have a huge potential in creating successful topical pharmaceutical formulations.

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### Modular Assembly of Immune Signals into Polyelectrolyte Multilayers to Promote Immunological Tolerance

Lisa H. Tostanoski,<sup>a</sup> Boyan Xia,<sup>a</sup> Yu-Chieh Chiu,<sup>a</sup> James I. Andorko,<sup>a</sup> Ming Guo,<sup>b,c</sup> Xiangbin Zeng,<sup>a</sup> Peipei Zhang,<sup>a</sup> Walter Royal III,<sup>b,c</sup> and Christopher M. Jewell<sup>a,d-f</sup>

### Introduction

During autoimmune diseases, such as multiple sclerosis (MS), the body incorrectly recognizes and attacks "self" tissues. Conventional clinical therapies for MS employ broad immunosuppression, which has provided important benefits for patients but is noncurative and can compromise healthy, protective immune function.<sup>1</sup> In contrast, experimental therapies aim to reprogram how the body responds specifically to myelin—the self-molecule attacked in MS—while leaving the rest of the immune system intact. One approach toward this goal has been the coadministration of self-antigens and regulatory signals that could bias differentiating immune cells toward regulatory functions and phenotypes, instead of inflammatory populations.<sup>2–4</sup> New studies in mouse models and human autoimmune disease reveal that excess signaling through inflammatory pathways, such as toll-like receptors (TLRs), contributes to disease.<sup>5–10</sup> Thus, we hypothesized that codelivery of a regulatory TLR9 ligand, GpG,<sup>11–12</sup> with myelin peptide could reduce TLR-driven inflammatory cues that expand self-reactive T cells, instead promoting regulatory T cells ( $T_{REGS}$ ) that control disease in a myelin-specific manner.

Biomaterials can enable codelivery, while offering other attractive features—tunable loading and cargo protection, for example—that support *in vivo* delivery of therapeutics.<sup>2-4</sup> However, many biomaterials also exhibit intrinsic inflammatory features that could exacerbate autoimmune disease.<sup>13-15</sup> Thus, we designed immune polyelectrolyte multilayers (iPEMs) as nanostructured assemblies that mimic attractive features of biomaterials but are composed entirely of immune signals. Because no other polymers, matrices, or carrier components are needed, iPEMs allow simple, modular assembly of peptide antigens and regulatory signals at very high cargo densities. As described in our recent report, self-antigens and GpG can be assembled into iPEMs using electrostatic interactions without compromising the selectivity of molecular interactions.<sup>16</sup> Further, iPEMs promote tolerogenic phenotypes and function in mouse cells *in vitro* and *in vivo*, restrain disease in a mouse model of MS, and control inflammation in human MS patient samples.<sup>16</sup> Below, we highlight some of these findings, as well as our ongoing work to incorporate controlled release capabilities into the iPEM platform.

#### **Experimental Methods**

iPEMs composed of myelin peptide fragments conjugated to tri-arginine to confer positive charge (MOG-R<sub>3</sub>), and either a regulatory TLR9 ligand, GpG, or an irrelevant control oligonucleotide (CTRL) were deposited on either planar (i.e., silicon or quartz) or colloidal (i.e., calcium carbonate microparticle templates) substrates in a layer-by-layer fashion. Layer-dependent growth of iPEMs was quantified using ellipsometry, UV/Vis spectrophotometry, and fluorescence microscopy. In some experiments, myelin peptide was replaced with a degradable poly(beta amino ester) to facilitate controlled release of immune cargo from iPEMs. In studies on colloidal substrates, sacrificial microparticle templates were removed after assembly by incubation in 0.1M ethylenediaminetetraacetic acid (EDTA), followed by a phosphate-buffered saline (PBS) wash before use in cell or animal studies.

For *in vivo* studies, mice were induced with a common model of MS, experimental autoimmune encephalomyelitis (EAE), and either left untreated or treated subcutaneously with iPEMs. Mice were monitored for clinical symptoms of disease (i.e., paralysis) and weight loss using protocols approved and overseen by the University of Maryland, College Park, Institutional Animal Care and Use Committee in compliance with local, state, and federal guidelines. At the indicated time points, cells from the spleens were isolated and analyzed for the frequency of  $T_{REGS}$  and myelin-triggered secretion of inflammatory cytokines.

Human MS patient peripheral blood mononuclear cell (PBMC) samples were collected in conjunction with the Institutional Review Board-approved VALOMS study protocol with informed signed consent. VALOMS is an observational study that has been initiated

continued

<sup>&</sup>lt;sup>a</sup> Fischell Department of Bioengineering, University of Maryland, 8228 Paint Branch Drive, College Park, MD 20742, U.S.A.

<sup>&</sup>lt;sup>b</sup> Department of Neurology, University of Maryland School of Medicine, 655 West Baltimore Street, Baltimore, MD 21201, U.S.A.

<sup>&</sup>lt;sup>c</sup> Multiple Sclerosis Center of Excellence–East, U.S. Department of Veterans Affairs, 655 West Baltimore Street, Baltimore, MD 21201, U.S.A.

<sup>&</sup>lt;sup>d</sup> Department of Microbiology and Immunology, University of Maryland Medical School, 685 West Baltimore Street, HSF-I Suite 380, Baltimore, MD 21201, U.S.A.

<sup>&</sup>lt;sup>e</sup> U.S. Department of Veterans Affairs, 10 North Greene Street, Baltimore, MD 21201, U.S.A.

<sup>&</sup>lt;sup>f</sup> Marlene and Stewart Greenebaum Cancer Center, 22 South Greene Street, Baltimore, MD 21201, U.S.A.

#### Scientifically Speaking Tostanoski continued

by the Department of Veterans Affairs Multiple Sclerosis Center of Excellence–East to examine factors associated with disease progression among U.S. military veterans with MS. Frozen PBMC samples selected randomly from the patient sample repository were thawed, washed, and incubated with tolerogenic or control iPEMs, or in media alone. Cultures were then analyzed for metabolic activity (MTT) and cytokine secretion via a Luminex multianalyte system.

#### **Results and Discussion**

**iPEM Assembly and Characterization.** MOG-R<sub>3</sub> and GpG were assembled in a layer-by-layer fashion to form iPEMs (Fig. 1A). Fluorescence microscopy confirmed colocalization of both cargos (Fig. 1B), while ellipsometry and spectrophotometry revealed an increase in iPEM thickness (Fig. 1C) and relative cargo loading (Fig. 1D), respectively, as a function of the number of bilayers deposited on planar substrates. To explore the potential for controlled release of immune cargos from iPEMs, in some studies, myelin peptide was replaced with a cationic, degradable polymer (Fig. 1E). Spectrophotometry revealed an increase in cargo loading during iPEM assembly (Fig. 1F), followed by a subsequent decrease in loading upon incubation of iPEMs in buffer (Fig. 1G). These results demonstrate the flexibility and modularity of this platform.



Figure 1. Tunable assembly and characterization of iPEMs on planar substrates. (A) Schematic of layer-by-layer assembly of myelin self-antigen  $(MOG-R_{,})$  and a TLR9 antagonist (GpG) to form iPEMs. (B) Fluorescence microscopy images of quartz substrates, following deposition of eight MOG-R<sub>1</sub>/GpG bilayers (green, FITC-MOG-R<sub>2</sub>; red, Cy5-GpG; scale, 20  $\mu$ m). A needle was used to remove a portion of the film to provide contrast (dotted white lines). Atomic force microscopy analysis of the surface morphology of (MOG-R/GpG)<sub>s</sub> iPEMs (x-y scale, 3 µm; z scale, 400 µm). (C) Stepwise measurements of iPEM thickness with increasing numbers of  $MOG-R_{4}/GpG$  bilayers deposited on silicon substrates, quantified by ellipsometry. (D) Spectrophotometric analysis of relative loading of MOG-R, (500 nm) and GpG(260 nm) as a function of the number of bilayers deposited on quartz substrates. (E) To facilitate controlled release of cargos, myelin self-antigen was replaced with a degradable poly(beta amino ester), polymer 1. (F) Relative loading of GpG in Poly1/GpG iPEMs was measured by spectrophotometry as a function of the number of layers deposited. (G)(Poly1/GpG)<sub>10</sub> iPEMs were incubated in PBS, and cargo loading was measured at indicated time points. Spectrophotometric measurements indicate that GpG loading decreases over time. Data represent mean  $\pm$  SEM (n = 3). Panels A-D adapted from Tostanoski et al.<sup>16</sup>

To facilitate cell and animal studies, MOG-R<sub>3</sub>/GpG iPEMs were next deposited on sacrificial calcium carbonate microparticles. Fluorescence microscopy images indicated an increase in cargo loading as a function of the number of layers, which was confirmed quantitatively via pixel intensity analysis (Fig. 2A). Next, the relative input of immune cargos was varied, resulting in iPEMs with tunable relative loading of MOG-R<sub>3</sub> and GpG (Fig. 2B). Following assembly of iPEMs, microparticle templates were dissolved, leaving hollow capsules composed entirely of either myelin and GpG, or myelin and an irrelevant control oligonucleotide (Fig. 2C). Together, the data above demonstrate that iPEMs can be assembled in a programmable manner, motivating studies to investigate the tolerogenic potential.

iPEMs Restrain Inflammation, Promote T<sub>REGS</sub>, and Halt Disease in a Model of MS. To explore the impact of iPEMs on immune cell function and phenotype in vivo, mice were induced with EAE and either left untreated or administered iPEMs on days 5 and 10 post-induction (Fig. 3A). As expected, restimulation of cells from the spleens of induced, untreated mice with myelin peptide triggered high levels of inflammatory interleukin 17 (IL-17) (Fig. 3B), interferon-γ (IFN-γ) (Fig. 3C), and interleukin 6 (IL-6) (Fig. 3D) secretion compared with cells pulsed with irrelevant peptide (i.e., OVA<sub>323-339</sub>). In contrast, restimulation of cells from iPEM-treated mice resulted in low levels of cytokine secretion, even during restimulation with myelin peptide, indicating a reduced inflammatory response to self-antigen (Fig. 3B–D). In similar studies, cells from the spleen were analyzed immediately (i.e., without restimulation) for the presence of T<sub>REGS</sub>, defined as CD4<sup>+</sup>/CD25<sup>+</sup>Foxp3<sup>+</sup> cells. iPEM treatment drove a significant increase in the frequency of T<sub>REGS</sub> (Fig. 3E–F). Finally, continued monitoring of mice treated as in Figure 3A revealed that induced, untreated mice exhibited significant EAE-induced paralysis (Fig. 3G) and weight loss (Fig. 3I). In contrast, iPEMs prevented disease in 100% of mice and inhibited disease-associated weight loss (Fig. 3G-I).

continued



**Figure 2.** Programmable assembly and characterization of iPEMs on colloidal substrates. (A) Representative images (top) and quantitative pixel analysis (bottom) of relative GpG loading with subsequent iPEM deposition cycles on a calcium carbonate microparticle core (red, Cy5-GpG; scale, 2  $\mu$ m). (B) Spectrophotometric quantification of tunable relative composition of iPEMs as a function of the relative input mass of MOG-R<sub>3</sub> and GpG into iPEM synthesis. Data represent mean ± SEM (n = 4 for each input ratio). (C) Representative fluorescence microscopy images of hollow iPEM capsules composed entirely of either MOG-R<sub>3</sub> and GpG (top) or MOG-R<sub>3</sub> and a nonimmunoregulatory oligonucleotide (CTRL, bottom), following removal of the calcium carbonate core by incubation in EDTA (green, FITC-MOG-R<sub>3</sub>; red, Cy5-GpG; magenta, Cy3-CTRL; scale, 2 µm). Adapted from Tostanoski et al.<sup>16</sup>



**Figure 3.** *iPEMs restrain pro-inflammatory immune cell function and progression of a model of autoimmunity in vivo. (A) Schematic of experiment timeline.* Mice were induced with EAE and either left untreated or administered two doses of MOG-R<sub>3</sub>/GpG iPEMs on days 5 and 10 post induction. On day 13, splenocytes from induced, untreated mice (n = 4) or iPEM-treated mice (n = 4) as in (A) were restimulated with either MOG (pulse: "M") or OVA<sub>323-339</sub> (pulse: "O") for 48 h, and ELISA was used to quantify peptide-triggered secretion of inflammatory (B) IL-17, (C) IFN- $\gamma$ , and (D) IL-6. (E and F) In similar studies, splenocytes were isolated (n = 4 for both groups) on day 13 and analyzed immediately for the frequency of CD4<sup>+</sup>/CD25<sup>+</sup> Foxp3<sup>+</sup> cells. To assess therapeutic efficacy of iPEMs, mice were induced with EAE and either left untreated (n = 11) or administered iPEMs (n = 10) as in (A) and monitored for (G) mean clinical score, (H) disease-associated weight loss, and (I) incidence of disease. In panels B- D, data were analyzed with one-way ANOVA with a Tukey post-test. In panel F, statistics indicate the results of a two-tailed t test. In panels G and H, data were analyzed with multiple t tests, one at each time point, with a post-test correction for multiple comparisons. Disease incidence in (I) was analyzed with a log-rank test. (\*, \*\*, \*\*\*, and \*\*\*\* = P ≤ 0.05, 0.01, 0.001, and 0.0001, respectively). Adapted from Tostanoski et al.<sup>16</sup>

iPEMs Attenuate Inflammatory Response in Human MS Patient Samples. To investigate the translational potential of iPEMs to human disease, we drew on an approach used in recent clinical trials: *ex vivo* restimulation of PBMCs from MS patients.<sup>17</sup> In our studies, we incubated PBMCs with either MOG-R<sub>3</sub>/GpG or MOG-R<sub>3</sub>/CTRL iPEMs to isolate any tolerogenic effects from inclusion of the TLR9 antagonist, GpG. MTT analysis revealed an increase in metabolic activity following treatment with either iPEM formulation (Fig. 4A). This result suggested the expected myelin-triggered increase in cell function associated with myelin-specific immune cells present during MS. However, despite similar levels of metabolic activity, GpG-containing iPEMs restrained inflammatory cytokine profiles compared with the control iPEM formulation. Excitingly, in nearly every case, tumor necrosis factor- $\alpha$ 

#### Scientifically Speaking Tostanoski continued

 $(TNF-\alpha)$  (Fig. 4B), IL-6 (Fig. 4C), IL-10 (Fig. 4D), and IFN- $\gamma$ (Fig. 4E) levels were lower when PBMCs were treated with MOG-R,/GpG iPEMs compared with MOG-R,/CTRL iPEMs, although the specific cytokines for which these decreases were statistically significant varied across patients.

### Conclusion

In our work, we have used three experimental systems-mouse cells, mouse models of MS, and human MS patient samples-to demonstrate that polyelectrolyte multilayer technology can be employed to promote immune tolerance. One of the unique opportunities with iPEMs and other tunable systems that permit controlled release is the ability to study how the kinetics of signal delivery impact the size or nature of immune response. Another ongoing direction is elucidation of whether late-stage treatment with iPEMs can reverse established disease in mice and drive remyelination in the central nervous system, critical criteria for experimental MS therapies. Further follow-up studies with statistically relevant sets of human patient samples could reveal the utility of iPEMs to combat human disease.

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Legend (all panels): ● Unstimulated ▲ (MOG-R<sub>3</sub>/GpG)<sub>3</sub> ■ (MOG-R<sub>3</sub>/CTRL)<sub>3</sub>

0

n

2.5

0

Figure 4. iPEMs activate human MS patient PBMCs but attenuate inflammatory cytokine secretion. (A) Metabolic activity of PBMCs from three randomly selected MS patients following incubation with either  $(MOG-R_{\prime}/GpG)_{3}$  or  $(MOG-R_{\prime}/CTRL)_{3}$  iPEMs for 72 h, measured via MTT analysis. For each patient, the metabolic activity of cells treated with each iPEM formulation was normalized to control wells of PBMCs incubated with media only (unstimulated). Supernatants of cultures were collected and analyzed via a Luminex multiplex assay to quantify the secretion of (B)  $TNF-\alpha$ , (C) IL-6, (D) IL-10, and (E) IFN-y. Data in all panels represent mean ± SEM (n = 3). Adapted from Tostanoski et al.<sup>16</sup>

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### Drug Delivery and Translational Research Update

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

#### DDTR Reached 100K Downloads in December 2016

We have been monitoring several parameters that reflect growth of the journal. We are pleased to announce that *DDTR*, which began publication in 2011, achieved an important milestone of reaching 100K cumulative downloads in December 2016. The increase in downloads has been almost exponential over the past two years, with around 313 downloads per article. With a new feature added, authors can track downloading of their publications in real time on the journal website. In this regard, I would like to highlight two recent special issues with the most articles downloaded.

- Microneedles for Drug and Vaccine Delivery and Patient Monitoring (volume 5, issue 4, pages 311-467, 2015). Guest editors: Ryan Donnelly and Dennis Douroumis (approximately 6,300 downloads)
- Ocular Drug Delivery (volume 6, issue 6, pages 631-815, 2016). Guest editors: Ilva D. Rupenthal and Michael O'Rourke (approximately 4,400 downloads)

Year	Downloads	
2011	5,609	
2012	9,654	
2013	16,050	
2014	13,915	
2015	22,062	
2016	39,881	
Total	107,171	

We are pleased to see that, just like CRS, the journal has a global reach, advancing drug delivery science and technology. We have received articles from over 40 countries, covering different aspects of translational drug delivery. We thank all the authors and reviewers for considering *DDTR* as their journal and making significant contributions. CRS members can access the articles published in *DDTR* as a membership benefit. Visit the CRS website to learn how (controlledreleasesociety.org/publications/ Pages/DDTR.aspx). Also, consider publishing your best research paper for the *DDTR* Outstanding Paper Award. To sign up for table of contents alerts, visit the *DDTR* website (springer.com/biomed/ pharmacology+%26+toxicology/journal/13346).

We are developing several special issues. Contact the respective guest editor if you would like to contribute an article.

- Drug Delivery and Female Reproductive Health. Guest editor: David Friend, Evofem Biosciences, Inc., U.S.A. (dfriend@evofem.com)
- Canadian Chapter of the Controlled Release Society. Guest editors: Michael R. Doschak, University of Alberta (mdoschak@ualberta.ca), Emmanuel A. Ho, University of Manitoba (Emmanuel.Ho@umanitoba.ca), and Christine Allen, University of Toronto (cj.allen@utoronto.ca)
- Novel Drug Delivery Systems, Devices, and Fabrication Methods. Guest editor: Vivek Agrahari, Bayer Pharmaceutical (vivek.agrahari@bayer.com)
- Cardiovascular Drug Delivery. Guest editors: Michael Chorny, Children's Hospital of Philadelphia (chorny@email.chop.edu), Gershon Golomb, Hebrew University (gershong@ekmd.huji.ac.il), and Robert J. Levy, Children's Hospital of Philadelphia (levyr@email.chop.edu) =

### **CRS Nordic Chapter Meeting**

Bente Steffansen,<sup>1</sup> Anette Larsson,<sup>2</sup> Gøril Eide Flaten,<sup>3</sup> Marika Ruponen,<sup>4</sup> and Ingunn Tho<sup>5</sup>

The CRS Nordic Local Chapter event this year was "The Nordic Innovative Drug Delivery Meeting," which was organized together with the Swedish Academy of Pharmaceutical Sciences, AstraZeneca, and others. The meeting was held in Sweden, partly at Chalmers University of Technology (CUT) in Gothenburg and partly at AstraZeneca in Mölndal, from June 1 to June 3, and gathered100 participants. The program was divided into six sessions with well-reputed invited speakers and speakers selected from the submitted abstracts. During the poster session 25 posters were presented.

The meeting was opened on Wednesday evening with registration followed by a welcome from the local organizer at CUT, Anette Larsson, and the CRS Nordic Local Chapter chair, Ingunn Tho (University of Oslo, Norway). Anette Larsson, CRS Nordic chapter board member and director of the VINN Excellence Centre SuMo Biomaterials (Supramolecular Biomaterials—Structure, Dynamics, and Properties) gave a presentation of the center's work on molecular transport in pharmaceutics. The next presentation was given by Ingunn Tho, who presented resent research on oromucosal drug delivery systems for children. The last presentation was given by Christer Tannergren from AstraZeneca on *in silico* modeling of gastrointestinal drug absorption, showing predictive performance of three physiologically based absorption models. The rest of the evening was dedicated to networking in a nice atmosphere with food and refreshments kindly provided by SuMo Biomaterials.

On the second day, the meeting moved to AstraZeneca's facilities. Organization committee leader Susanna Abrahmsén Alami, AstraZeneca, welcomed the delegates to the venue and chaired the session, starting with an invited lecture given by Gert Storm from Utrecht University, the Netherlands. He gave an inspiring lecture on theranostics in targeted nanomedicine development. The next invited speaker was Martin Malmsten from Uppsala University, providing insight into factors affecting peptide loading and release to



Atmosphere from the meeting (photos: Nina Lantz, AstraZeneca).

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

- <sup>2</sup> Chalmers University of Technology, Sweden.
- <sup>3</sup> UiT, The Arctic University of Norway.
- <sup>4</sup> University of Eastern Finland .
- <sup>5</sup> University of Oslo, Norway.

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### Nordic Chapter continued

and from microgels. After two early morning lectures it was time for a coffee break and the first look at the posters. The session continued with two short presentations selected from the submitted abstracts. First, Alex Bunker from University of Helsinki talked about new advances in computational approaches to the rational design of liposome-based delivery systems. Among other things, he showed computational modeling of PEGylated lipid membranes, providing new insight into physiological behavior of PEGylated nanoparticles. The next selected abstract was presented by Karin Norling, who is a Ph.D. student at CUT. She talked about properties and cellular uptake characteristics of liposome-based mucosal vaccines. The morning session was concluded by a short poster presentation, where all presenters were given two-minute slots to introduce the poster from the stage. After the poster teaser, lunch was provided in the AstraZeneca restaurant.

Session 3 was initiated by Anette Müllertz from University of Copenhagen, whose abstract (authored by Mette Klitgaard, Philip Jonas Sassene, Liza Al-Muhanna, and Anette Müllertz) was selected for oral presentation. Anette gave an interesting talk about their latest dissolution results on selected "grease ball" APIs and showed that these APIs' dissolution better correlated to *in vivo* preclinical bioavailability in beagle dogs when dissolution was studied in the developed two-step step model compared with a conventional single-step model. The next selected abstract (authored by Johanna Andersson, Anna Ström, and Anette Larsson from CUT) was presented by Anna Ström and was concentrated on capillary flow phenomenon using hydrogels (2% alginate and agarose) as a solid

wall. She discussed how these systems form empty capillaries within the gels and how these empty capillaries after connecting to a drop of water were filled with water within seconds, driven by capillary pressure, which plays a major role in many processes such as tablet disintegration and film formation. The session was then continued by presentations of research collaborations between small companies and academia. Helena Bysell from SP Technical Research Institute of Sweden presented interesting results from the FORMAMP project, which is an interdisciplinary project funded by EU 7th Framework Programme (FP7). Helena showed that the antibacterial effect of antimicrobial peptides could be maintained when formulated as nanoparticles of carrier-peptide combinations. Louise Zettergren from VISCOGEL AB presented result from their chitosan-based hydrogel formulations (ViscoGel<sup>™</sup>). The formulations were aimed as slow-release drug delivery systems for biologicals, and Louise showed how the *in vitro* release rate of the model (bovine serum albumin) depended on the ViscoGel<sup>™</sup> formulation. Stefan Grundén from LIDDS in Uppsala presented results on their drug delivery technology for slow-release depot of cytostatic drugs exemplified with docetaxel.



Invited speaker Bente Steffansen.

After a well-deserved coffee break, the program continued with the invited presentation from Bente Steffansen from University of Southern Denmark. She gave an updated overview of membrane transporters in intestinal absorption and renal clearance with a physiologically based pharmacokinetic (PBPK) modelling approach for acamprosate. Finally, it was time for the award ceremony of the Gunnar Källrots Stipend, which is a scientific prize given by the Swedish Academy of Pharmaceutical Sciences every four years. The prize for 2016 was awarded to Conny Bogentoft for his extraordinary contribution to pharmaceutical development and industry in Sweden over decades. His award lecture reflected the huge developments of the discipline as well as the pharmaceutical industry in Sweden. This was a nice way to end the scientific program for the day and enjoy some outdoor refreshments in the beautiful summer evening before the conference dinner.

The third and last day of the conference was opened with a session comprising two invited speakers and was chaired by Nicholas Schipper from SP Process Development. Peter Languth from the University of Mainz started with a talk entitled "Dosage Form Aspects in Oral Bioavailability and Bioequivalence." He gave a nice historical view on development of oral formulations and drug delivery systems, from pills to nanotechnology, before he went in to systemic bioavailability. Here he focused on prolonged and delayed release, exemplified with some case studies from his research. He also shared his experience of how to get from concept to clinical phase I. Johan Engblom from Malmö University continued with an inspiring talk entitled "10 Microns Thick—How Hard Can It Be to Penetrate Skin?" He excellently explained the importance of the *stratum corneum* by using peeled and unpeeled cucumbers as easy-to-understand examples.

### Nordic Chapter continued



Invited speaker Johan Engblom.

Session 6 was chaired by Erik Bjork from Uppsala University and was opened by invited speaker Susanne Frydenberg from Novo Nordisk. She presented the challenges to formulating a protein product with high patient compliance, discussing the dilemma that either the formulations are acceptable for the patients but show low efficacy, or the other way around. Her main focus was formulations for low-frequency injections. Then it was time for three presentations selected from the submitted abstracts. Gøril Eide Flaten (UiT, The Arctic University of Norway) gave a talk entitled "The Phospholipid Vesicle-Based Permeation Assay (PVPA) to Determine Drug Permeability from Across Different Biological Barriers," where she presented the development of *in vitro* permeability models for the two biological barriers, intestinal epithelia and skin/stratum corneum. Marianne Yanez Arteta from AstraZeneca presented a talk entitled "Lipid Nanoparticles for mRNA Delivery: Structural Determination and In Vitro Efficacy." Arteta elaborated on the questions: Why do we need lipid nanoparticles for mRNA delivery? And how should we characterize the structure of these particles? Staffan Schantz, also from AstraZeneca, continued on

the topic of structural characterization of nanoparticle systems with his talk "New NMR Methods for Characterization of siRNA Encapsulated Lipid Nanoparticles."

The last and extensive after-lunch session was chaired by Jonas Jonassen from AstraZeneca. Invited speaker Hans Lennernäs from Uppsala University got the honor of having the challenging first talk after lunch, which he managed excellently. Lennernäs guided us through several important topics: regional intestinal permeability in humans, variability in absorption after oral administration, and effect of changes in motility as well as endocrinology. The next invited speaker was Anne Juppo from the University of Helsinki, who introduced atomic layer deposition (ALD) as a novel technology for nanocoating of both drug powders and minitablets. ALD was shown to provide controlled coating and, based on preliminary studies, was able to modify drug release profile, mask taste, and improve structural stability and processability of drugs. However, despite its potential the technology still requires a lot of basic research and understanding. The next speaker was Joel Hellrup, a Ph.D. student from Uppsala University, who had utilized the same ALD-based technology for coating. This coating, termed as PharmaShell<sup>®</sup>, was shown to prevent moisture sorption and improve the long-term stability of amorphous lactose. In the case of amorphous sulindac, the coating was not able to prevent but only delay the dissolution of sulindac. The last but definitely not least speaker in the meeting was Gordon Amidon from the University of Michigan. Gordon introduced the recent progress in the development of *in vivo* predictive dissolution testing funded by the FDA. He stated, for example, that the current Biopharmaceutics Classification System classes are not adequate, but new subclasses in terms of dissolution should be added under each of the major classes.

To conclude the meeting, Johanna Andersson, a Ph.D. student from CUT, was presented with the prize for the best poster for her clear and scientifically sound presentation entitled "Spontaneous Liquid Penetration of Capillaries in Semi-solids." Susanna Abrahmsén Alami and Ingunn Tho thanked the organizers, the presenters, and all the delegates for a fruitful meeting. Next Nordic Local Chapter meeting will be in Kuopio, Finland, in June 2017.

### **Drug Delivery Australia 2016**

Patrick Spicer, University of New South Wales, Australia

The Annual Meeting of the CRS Australian Local Chapter, Drug Delivery Australia 2016, took place on the University of New South Wales (UNSW), Australia, main campus October 27 and 28. The meeting was attended by 95 delegates from over 30 academic and industrial institutions. The meeting theme was "Particles to People," and the talk tracks were organized according to elements of delivery via different suspended, aerosolized, and fundamental forms of active materials and delivery matrices.

The meeting included plenary lectures from Gert Storm (Utrecht University, the Netherlands) and Martina Stenzel (UNSW Australia), as well as an excellent slate of invited international speakers including Kok Ping Chan (ASTAR, Singapore), David Cipolla (Aradigm, U.S.A.), and Shakila Rizwan (Otago University, New Zealand).



Attendees mill about during the coffee break.

The conference also offered a great opportunity to showcase a diverse group of

Australian researchers in Drug Delivery with invited talks from Sophia Gu (UNSW Australia), Kara Perrow (University of



Sophia Gu presents an invited talk. Hui Xin Ong presents.

Wollongong), Heather Benson (Curtin University), Hui Xin Ong (Woolcock Institute), Josh McCarroll (Children's Cancer Institute), Nicky Thomas (University of South Australia), and Kris Thurecht (University of Queensland), as well as others. The conference dinner was extremely popular: a harbour cruise with dinner and drinks on the first night of the conference.

In addition to talks, over 50 posters were presented throughout the conference, allowing discussion, networking, and enjoyment of the outdoor environment of the meeting venue. The top eight poster presenters were chosen for a rapid-fire "Poster to Podium" session on the second day, with each speaker given three minutes to summarize and "pitch" their work to a broad audience, using only one slide and NO animations. The session was a fun, enthusiastic one with many excellent performances and demonstrations of time management.

The judges chose two winners for the Poster to Podium presentations—Giulia Ballerin (University of Technology Sydney) and Shadabul Haque (Monash University)—who each received a bursary to attend the CRS Annual Meeting in Boston in 2017.

An additional poster prize was kindly provided this year by Laura Fisher of the Royal Society of Chemistry. Three presenters were chosen to receive one-year subscriptions to the journal *Biomaterials Science*. The three winners of the RSC poster awards were Kristel Tjandra (UNSW Australia), Isha Haridass (Curtin University), and Younus Mohammad (Otago University).

Corporate sponsors, mostly instrument vendors, attended both days of the conference and were engaged in discussions during coffee breaks and poster sessions throughout the meeting.

A summary of the final conference program and the meeting details is archived on the CRS Australia website for reference: www.crsaustralia.org.



Poster winner Giulia Ballerin.



Poster winner Shadabul Haque.

### Pharmaceutical Innovations: Academia Meets Industry

Marco Adami,<sup>1</sup> Piero Iamartino,<sup>1</sup> and Bice Conti<sup>2</sup>

The ninth annual CRS Italy Local Chapter workshop, "Pharmaceutical Innovations: Academia Meets Industry," was held in Milan on November 3–4, 2016. About 80 delegates attended the meeting, coming from both academia and the pharmaceutical industry. The congress was held in the historic Napoleon Hall, University of Milan, in the center of Milan.

Promoting collaboration between academia and the pharmaceutical industry has been one of the objectives of the CRS Italy Local Chapter since its foundation. Recognizing that this cooperation is crucial to promote innovation in all stages of the drug development process, the 2016 workshop was focused on pharmaceutical innovation with speakers coming from both the pharmaceutical industry and academy. All topics were related to the three general areas: 1) formulation and technology, 2) equipment, and 3) technology and engineering, of course with overlaps between these areas.

The 2016 workshop consisted of lectures from invited speakers, all of them outstanding international scientists or industry representatives with recognized expertise in the field of pharmaceutical innovation. Each speaker was given 30–35 minutes to give a lecture, followed by focused discussion. General discussion also took place at the end of each day. As is the tradition of the workshop, shorter technical lectures were included as well, given by the meeting sponsors. Dedicated chairs coordinated and introduced all sessions and promoted the discussion.

In consideration of the scope of the workshop, Pablo Panella, who is a member of the board of Farmindustria, the Italian association of pharmaceutical industries, was invited to join the opening of the workshop, giving an introductory speech. He emphasized the importance of innovation in the pharmaceutical field, being an essential element for competition. He highlighted the growing position

of the Italian pharmaceutical industry in the manufacture and exportation of medicinal products, which is based on technological capabilities and knowledge, requiring a constant collaboration between industry and university.

Salvatore Mascia (CONTINUUS Pharmaceuticals, U.S.A.) gave the first lecture, entitled "Integrated Continuous Manufacturing of Pharmaceuticals." He introduced the revolutionary concept of integrated continuous manufacturing, based on the integration of chemical and pharmaceutical operations. Reactors that can handle solids, clean-in-place systems, tailored crystallization processes, and coprocessing of polymeric excipients and active pharmaceutical ingredients (APIs) into homogeneous solid dosage forms can all be integrated into a modular, plug-and-play line, which can indeed open a new manufacturing paradigm for the industry.

Marco Sanvito (BioPharmaceuticals Division, Pall Life Sciences, Italy) gave a lecture on "Technology Advances Enabling Integrated Continuous BioProcessing." The



Invited speaker Salvatore Mascia.

speaker provided a clear overview of an integrated bioprocessing platform, highlighting some of the advantages of the single-unit technologies, such as improved efficiency, lower costs, increased sterility assurance level, and less operator-dependent operations.

Alice Melocchi, representing a research group of the University of Milan, gave a presentation on "Application of Injection Molding and 3D Printing by Fused Deposition Modeling to the Manufacture of Drug Products." Her presentation was focused on the manufacture of a delivery system platform in the form of a capsular device, highlighting how the performance of this capsular device depends on its composition and design features, in spite of differing characteristics of the conveyed formulation, thus offering advantages in terms of time and costs of development. Next to injection molding, the application of 3D printing by fused deposition modeling, which enables

<sup>1</sup> Associazione Farmaceutici Industria, Milan, Italy.

<sup>&</sup>lt;sup>2</sup> University of Pavia, Italy.

#### Italy Chapter continued

the fabrication of solid objects of almost any shape, was described. This new technological approach could become a rapid prototyping tool in the development of swellable/erodible capsular devices for oral pulsatile release systems, with important savings in terms of time and costs of development. Furthermore, such a technique has been proposed to fulfill the need of personalized medicines because it allows the preparation of small batches of delivery systems, according to the required treatment of a small group of patients.



Peter Kleinebudde presents.

"Encapsulation of Liquids via Extrusion" was the title of the talk given by Peter Kleinebudde (Heinrich Heine University of Düsselsorf, Germany). This was an interesting lecture because extrusion, although well known in the food field, is not yet a consolidated technology in the pharmaceutical industry. The speaker showed how extrusion techniques could encapsulate liquids (e.g., essential oils, flavours, or APIs) into a carbohydrate matrix consisting of mixtures of sucrose with maltodextrin aimed at improving shelf life and handling as well as tailoring release.

Nadia Tagnaouti (Precision NanoSystems, Canada) and Enrica Chiesa (Polymerix srl/University of Pavia) shared a presentation about "Discovery, Development, Scalability, Clinics—Thinking Forward with the NanoAssemblr Platform."They presented the NanoAssemblr benchtop formulation system: using a proprietary microfluidics technology, it enables controlled, bottom-up, molecular self-assembly of

nanoparticles through millisecond mixing of components at nanolitre scale. This innovative technology gives researchers reproducibility and ease of use for iterating on nanoparticle design and therapeutic delivery experiments. The NanoAssemblr benchtop is capable of formulating 1–20 mL, which is ideal for low-cost formulation and process development. Scale-up is accomplished by parallelizing the microfluidic cartridges. A case study was presented to give practical evidence of the system.

"Platforms for Wound Reparation" was the lecture presented by Giuseppina Sandri (University of Pavia). It covered the development of formulations involved in dressings and scaffolding capable of covering a lesion, maintaining hydration and absorbing excess fluids, and forming a barrier against microbial contaminants and releasing antimicrobial agents. The presentation was focused on powders based on clay and nanocomposites (montmorillonite/chitosan and halloysite/chitosan), nano-emulsions, dressing (sponge-like systems delivering solid lipid nanoparticles, sponge-like systems delivering micelles, beads loaded with Manuka honey), and scaffolds (spongelike systems and nanofibers). The results of the *in vitro* biocompatibility and *in vivo* evaluation of the most promising formulations were presented.

The presentation of an innovative polymeric antioxidant, to be used as skin-whitening agent, was made by Francesco Puoci (University of Calabria), with the title "Beyond the Article: How to Move from Scientific Research to the Product." The preparation of this antioxidant polymer, being the result of a conjugation of dextran with rosmarinic acid, was described, presenting experimental data about its *in vitro* antioxidant activity, its tyrosinase inhibitory action, its stability, and the results of *in vivo* studies on 20 female s subjects clinically showing its whitening and lightening efficacy. It was highlighted that this innovative polymer, based on its long-lasting efficacy combined with to an enhanced stability, can be successfully used in cosmetic formulations as a bioactive ingredient. Flavio Fabiani (Novartis Pharma AG) gave a lecture entitled "NCE's Development Strategy: Decision Criteria for Selecting Traditional or Enabling Technologies." When dealing with poorly aqueous soluble drugs, enabling technologies are most often required to develop a solid dosage form. Because these technologies are significantly more costly, time-consuming, and risky than conventional technologies, the selection of the enabling technology most appropriate for the specific API under development becomes crucial for the pharmaceutical scientist. The speaker showed that the Biopharmaceutical Classification System (BCS) is the foundation for making the right decision, along with API-related technological factors, such as melting point, thermal stability, and solubility in organic solvents. The thorough evaluation of BCS-related and technological factors will lead to defining a decision tree for selecting the most suitable approach.

"Hyaluronic Acid Based Hydrogels for Antibiotic and Enzyme Release: From Academic Research to Industry" was the topic of the presentation by Fabio Palumbo (University of Palermo). In particular, two hyaluronic acid (HA) derivatives were presented. The first

### Italy Chapter continued

one was a graft copolymer of HA with poly-DL-lactic acid (PDLLA), showing an antibacterial activity for orthopaedic applications (Disposable Antibacterial Coating, DAC<sup>®</sup>). The second one was a photocrosslinkable HA derivative that is proposed for oral enzyme therapy in celiac disease. The chemical procedure used to functionalize HA and to prepare the two derivatives was described. *In vivo* studies (rabbit model) demonstrated hydrogel biocompatibility and confirmed antibacterial potential of DAC<sup>®</sup>, when it is used as a medicated hydrogel, easily spreadable over the surface of the prosthesis. The photocrosslinkable HA derivative was designed to entrap an enzyme (propyl endopeptidase, PEP) during UV crosslinking, to generate a hydrogel able to protect PEP from alteration, thus allowing its application in an oral formulation for treatment of celiac disease.

Ilona Pescher (Meggle) gave a lecture entitled "Sustained Release Formulation: Synergies in Manufacturing and Performance." In her lecture, she illustrated the properties of RetaLac, a Meggle coprocessed spray agglomerate consisting of equal parts of  $\alpha$ -lactose monohydrate and hypromellose (both Ph. Eur./USP-NF/JP). This excipient has been specifically designed for direct compression and dry granulation modified release formulations in which API release is controlled predominately by diffusion through the hydrophilic matrix.

Roberto Pisano (Polytechnic University of Turin) gave a lecture entitled "Quality by Design in Process Development and Scale-up for Lyophilized Parenteral Products." The speaker presented a non-steady state mathematical model, parameterized with experimentally



CRS annual workshop delegates in historic Napoleon Hall.

determined heat and mass transfer coefficients, which was used to manipulate the critical process parameters within predefined limits of the "design space." Calculations also recognized equipment and product constraints. Mathematical modeling was finally used to expedite scale-up operations, to transfer lyophilization cycles from smallscale equipment to manufacturing scale. Thus, the use of mathematical modeling would be effective not only for cycle development but also for minimizing the problem of process transfer, which is troublesome in the pharmaceutical industry.

The presentation of Sergio Mauri (Fedegari) about "Robotics in Process Automation: Present and Future" was mainly focused on the use of robotics in aseptic manufacture, which is considered one of the most challenging processes in pharmaceutical application. The speaker highlighted that the future of aseptic manufacturing is now also linked to a different model of development more focused on personalized medicine with small batches, short

runs, and the highest possible process flexibility. That is why Fedegari's 2020 goal will be a "cluster tool" arrangement with GMP stainless steel robot arms connecting different processes and technologies. There will be no human intervention, with gloveless isolators and a thorough grade A continuity, which will allow the overall sterility assurance level of the aseptic process to be enhanced to the level of the terminal sterilization level. Ultimately, this will provide the patients with more effective and safer drugs.

In conclusion, the workshop offered a good mix of academic and industrial lectures, all of them innovation oriented, in line with the meeting objectives. Participants appreciated the workshop program, and there were fruitful discussions both at the end of each lecture and during the final general session. Promoting and strengthening the collaboration between academic institutions and the pharmaceutical industry has always been an objective of CRS Italy Local Chapter, and the success of this year's workshop gave the organizers the stimulus to continue on this road.

The workshop was supported by CRS and generously sponsored by Evonik, QI Technologies, Harke, MP Strumenti, Meggle, Alfatest, PolyCrystalline, B&D Italia, Nordtest, and Macrofarm.

### **People in the News**

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

#### **Renowned Bioengineer to Join Harvard Faculty**



Harvard University: January 23, 2017 – CAMBRIDGE, MA, U.S.A. – Samir Mitragotri, a leading chemicaland bio-engineer who develops new techniques and materials for treating conditions such as diabetes, cancer, and bleeding disorders, will join the faculty of the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS). He is currently the Mellichamp Professor in the Department of Chemical Engineering at the University of California, Santa Barbara, where he is the founding director of the Center for Bioengineering.

Mitragotri will join SEAS in July as the Hiller Professor of Bioengineering and Wyss Professor of Biologically Inspired Engineering. He will also be a core faculty member of the Wyss Institute for Biologically Inspired Engineering at Harvard.

In modern medical practice, needles and syringes are the most common way of administering macromolecular drugs. Mitragotri has developed pioneering technologies to noninvasively deliver medicines using skin patches. Skin is a tough barrier; its purpose is to prevent drug transport rather than facilitate it. Mitragotri conducted pioneering research on skin's barrier function and developed techniques to successfully overcome it to allow delivery of biopharmaceutical drugs.

Mitragotri has also developed nanoparticles that can target tumors for the treatment of cancer, materials that can deliver proteins orally for diabetes, and synthetic analogs of blood components that can deliver medicines for bleeding disorders. Several of his inventions have been translated into clinical products.

"I am excited to join SEAS. Its interdisciplinary scholarly community offers outstanding opportunities to advance bioengineering research and education," Mitragotri said. "I am also looking forward to closely interacting with the communities at Harvard Medical School and the Wyss Institute to accelerate clinical and commercial translation of research."

Frank Doyle, the John A. Paulson Dean of SEAS, said: "Samir will bring a unique combination of experiences—bioengineering research, university leadership, and entrepreneurial activities—which will accelerate our strategic partnerships with Harvard Business School and Harvard Medical School."

Mitragotri's research also emphasizes understanding transport processes of biomolecules across biological barriers. "Fundamental understanding of biological barriers empowers us to develop knowledge-driven technologies to overcome them. We can't fix what we don't understand," Mitragotri said.

Mitragotri received his undergraduate degree from the Institute of Chemical Technology in Mumbai and Ph.D. from Massachusetts Institute of Technology under the mentorship of Profs. Robert Langer and Daniel Blankschtein. He is the author of more than 210 publications in the area of drug delivery and biomaterials, has given close to 500 invited and contributed presentations worldwide, and is an inventor on more than 150 pending or issued patents. He is a cofounder of several companies that are developing therapeutic or diagnostic products based on his inventions.

Mitragotri is an elected member of the National Academies of Engineering and Medicine and an elected fellow of the American Institute of Medical and Biological Engineering, the American Association for the Advancement of Science, the National Academy of Inventors, the Controlled Release Society, the Biomedical Engineering Society, and the American Association of Pharmaceutical Scientists. He is a Thomson Reuters Highly Cited Researcher. He serves on the editorial boards of several journals and currently serves as editor-in-chief of *Bioengineering and Translational Medicine*.

### **Companies in the News**

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

### January

### Nonopiate Painkiller, AnestaGel, Found Superior in Preclinical Tests

PRNewswire: January 25, 2017 – ST. PAUL, MN, U.S.A. – InSitu Biologics, LLC ("InSitu" or "the company"), an emerging drug delivery company focusing on development of new and proprietary treatments using its Matrix<sup>™</sup> BioHydrogel, today announced results from recent preclinical studies for their lead product, AnestaGel<sup>™</sup>. AnestaGel is a long-lasting and long-acting nonopiate painkiller, targeted for use in peri-operative regional pain management.

In a series of independent tests performed under GLP regulations, comparing operative site injections of AnestaGel and EXPAREL<sup>®</sup> from Pacira, Inc., AnestaGel was proven to last longer and to provide a greater analgesic effect than EXPAREL. In a separate test that determines the pharmacokinetic (PK) effect for the painkiller bupivacaine, which is used in both AnestaGel and EXPAREL, bupivacaine was proven to be released from AnestaGel into the blood up to 96–120 hours after injection, exceeding the presence of bupivacaine in the blood from both EXPAREL and straight bupivacaine injections.

"As we had hypothesized going in to these studies, we expected that AnestaGel would perform very well when compared to the nonopiate products available today," said Dr. Jake Hutchins, director of the Regional Anesthesia Acute Pain and Ambulatory Surgery division at the University of Minnesota, and the preclinical study director for InSitu Biologics. James Segermark, CEO of InSitu added, "Early on we believed that AnestaGel could be tuned to act as a short-term reservoir, essentially a nonpulsatile organ, and that is what we have now verified and validated. We look forward to the next steps that will bring this predictable, very long-acting, nonopiate product to patients that face the prospect of postsurgical pain." The company believes that AnestaGel could be used in three distinct markets for peri-operative pain management that represent nearly \$31 billion in annual revenue in the United States.

AnestaGel uses a novel approach to delivering sustained-released analgesics into the target tissue via the Matrix, which is a tunable, biocompatible, and pH neutral platform. This allows AnestaGel to provide target site-specific, nonmigratory placement, a flexible and high dose drug-load reservoir capacity, and a tunable and predictable pharmacological effect.

InSitu Biologics develops and manufactures implantable timed release products composed of our proprietary tunable, bio-polymeric hydrogel, Matrix<sup>™</sup>. We are currently pursuing applications for delivery in soft and bone tissue(s). For more information, please visit www.insitubiologics.com.

### Enteris BioPharma Enters into Agreement with Nordic Bioscience's KeyBioscience to Develop Orally Delivered Metabolic Peptide

PRNewswire: January 25, 2017 – BOONTON, NJ, U.S.A. – Enteris BioPharma, Inc., a biotechnology company developing innovative drug products built around its proprietary delivery technologies, today announced the initiation of a clinical manufacturing services agreement with KeyBioscience AG, a wholly owned subsidiary of Nordic Bioscience, whereby Enteris will leverage its proprietary Peptelligence<sup>™</sup> platform to advance the development of a proprietary metabolic peptide for the treatment of various indications, including diabetes, obesity, and other metabolic disorders.

Under the terms of the agreement, Enteris BioPharma will leverage its Peptelligence<sup>™</sup> platform to manufacture and characterize three oral tablet prototypes of KeyBioscience's metabolic peptide, as well as become the exclusive provider of finished product for use in preclinical and proof-of-concept clinical trial research.

Joel Tune, chief executive officer and executive chairman of Enteris BioPharma, commented, "This agreement with Nordic Bioscience showcases the value of our Peptelligence<sup>™</sup> platform to develop and enable the oral delivery of promising peptide and small molecule therapeutics. Additionally, it highlights our unique ability to partner with global pharmaceutical companies to develop drug products that address significant patient care and market opportunities. We are truly excited to be working with KeyBioscience on this new class of compounds."

Morten Karsdal, chief executive officer of Nordic Bioscience, remarked, "The ability to deliver our proprietary DACRA peptides orally offers KeyBioscience the potential to bring to market a new therapeutic choice for the treatment of metabolic disorders, which is a

significant market opportunity. An oral delivery using Enteris' Peptelligence<sup>™</sup> platform and manufacturing capabilities will be a value driver and a key to success. We look forward to progress with an oral formulation of our DACRA peptides into clinical trials and potential commercialization."

KeyBioscience develops and hold all rights to DACRA peptides for various metabolic and cartilage related diseases. KeyBioscience is a fully owned subsidiary of Nordic Bioscience, a global drug development organization headquartered in Copenhagen, Denmark. Nordic Bioscience is engaged in clinical research and innovative biomarker research focusing on connective tissue diseases. The capabilities and experience with research and development place Nordic Bioscience in a unique position to develop advanced specialized protocols to conduct innovative clinical studies from phase 1 to phase 3. Using a data-driven approach, Nordic Bioscience has a long history of applying novel technologies in translational and biomarker science promoting precision medicine, particularly within rheumatology.

For additional information please visit the company's website at http://nordicbioscience.com.

Enteris BioPharma, Inc., is a privately held, New Jersey–based biotechnology company offering innovative formulation solutions built around its proprietary drug delivery technologies. Enteris's proprietary oral delivery technology—Peptelligence<sup>™</sup>—has been the subject of numerous feasibility studies and active development programs, several of which are in late stage clinical development. Enteris BioPharma's most advanced internal product candidate, Ovarest<sup>™</sup>, an oral peptide for endometriosis, will begin phase 2A trials in the next quarter. For more information on Enteris BioPharma and its proprietary oral delivery technology, please visit www.EnterisBioPharma.com.

# Ocular Therapeutix™ Resubmits NDA for DEXTENZA™ for the Treatment of Ocular Pain Occurring After Ophthalmic Surgery

Business Wire: January 23, 2017 – BEDFORD, MA, U.S.A. – Ocular Therapeutix, Inc. (NASDAQ: OCUL), a biopharmaceutical company focused on the development and commercialization of innovative therapies for diseases and conditions of the eye, today announced that it has resubmitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for DEXTENZA<sup>TM</sup> (dexamethasone insert) 0.4 mg, for the treatment of ocular pain occurring after ophthalmic surgery. DEXTENZA is a product candidate administered by a physician as a bioresorbable intracanalicular insert and designed for drug release to the ocular surface for up to 30 days.

"Following productive discussions with the FDA, we are pleased to announce the resubmission of our NDA for DEXTENZA for the treatment of ocular pain occurring after ophthalmic surgery," said Amar Sawhney, Ph.D., president, chief executive officer, and chairman. "If DEXTENZA is approved, we believe that its ability to provide a complete course of steroid therapy with one-time administration in the postsurgical setting will be extremely attractive for both ophthalmologists and patients. We continue to build our commercial organization and infrastructure in preparation for the earliest possible launch of DEXTENZA, subject to marketing approval."

Ocular Therapeutix resubmitted the NDA in response to a complete response letter (CRL) the company received from the FDA in July 2016, which identified items pertaining to deficiencies in manufacturing process and controls. The company expects to receive an indication of the scope and timing of the FDA's review of the company's NDA resubmission within approximately 30 days. The company believes that the FDA review period of the NDA resubmission will be up to two months if a Class 1 (minor review) designation is received and up to six months if a Class 2 (major review) designation is received. Class 1 or 2 designation is dependent on whether an FDA reinspection of the Ocular Therapeutix manufacturing facility will be a condition of NDA approval.

DEXTENZA (dexamethasone insert) 0.4 mg is placed through the punctum, a natural opening in the eye lid, into the canaliculus and is designed to deliver dexamethasone to the ocular surface for up to 30 days. Following treatment, DEXTENZA resorbs and exits the nasolacrimal system without need for removal. The company has completed three phase 3 clinical trials with DEXTENZA for the treatment of postsurgical ocular inflammation and pain. Subject to the approval of the NDA for postsurgical ocular pain by the FDA, Ocular Therapeutix intends to submit an NDA supplement for DEXTENZA to broaden its label to include a postsurgical inflammation indication. DEXTENZA is also in phase 3 development for the treatment of ocular itching associated with allergic conjunctivitis.

Ocular Therapeutix, Inc. (NASDAQ: OCUL) is a biopharmaceutical company focused on the development and commercialization of innovative therapies for diseases and conditions of the eye using its proprietary hydrogel platform technology. Ocular Therapeutix has resubmitted an NDA for postsurgical pain for its lead product candidate, DEXTENZA™ (dexamethasone insert) 0.4 mg, which has completed phase 3 clinical development for postsurgical ocular inflammation and pain. Subject to the approval of the NDA for postsurgical ocular Therapeutix intends to submit a supplemental NDA for DEXTENZA to broaden its label to include

an indication for postsurgical inflammation. DEXTENZA is also in phase 3 clinical development for allergic conjunctivitis. OTX-TP (travoprost insert) is in phase 3 clinical development for glaucoma and ocular hypertension. Ocular Therapeutix is also evaluating injectable drug delivery depots for back-of-the-eye diseases. Ocular Therapeutix's first product, ReSure<sup>®</sup> sealant, is FDA-approved to seal corneal incisions following cataract surgery. For additional information about the company, please visit www.ocutx.com.

### PixarBio Corporation Terminates InVivo Therapeutics Bid

Business Wire: January 23, 2017 – CAMBRIDGE, MA, U.S.A. – PixarBio Corporation, (OTCQX: PXRB) today announced that we will stay focused on our NeuroRelease Pain platform and continue to drive our nonopiate nonaddictive morphine replacement to market with FDA approval expected between the end of 2018 and early 2019.

PixarBio has an IP portfolio covering pain, spinal cord injury, and epilepsy, and we believe that we will become future market leaders with our existing and growing PixarBio patent and IP portfolio for various drug delivery systems.

On behalf of the shareholders and board of directors of PixarBio we withdraw our offer for InVivo Therapeutics Corp. for reasons related to management credibility and competence, corporate governance, and IP control. For more information, please visit our investor relations page on our website, www.pixarbio.com, and click on the document entitled The Story Behind PixarBio's Termination of the InVivo Therapeutics Deal.

PixarBio is a public company traded on the OTC markets under the stock symbol PXRB. PixarBio is a specialty pharmaceutical/ biotechnology company focused on preclinical and clinical commercial development of novel neurological drug delivery systems for postoperative pain. PixarBio researches and develops targeted delivery systems for drugs, devices, or biologics to treat pain, epilepsy, Parkinson's disease, and spinal cord injury. Our lead product platform, NeuroRelease<sup>™</sup>, has achieved sustained therapeutic release of nonopiate drugs for postoperative, acute, and chronic pain in preclinical models. For more information, visit www.pixarbio.com.

# Cristal Therapeutics Raises €12.8 Million in New Financing Round to Advance Novel Medicines Against Cancer Using Its CriPec<sup>®</sup> Nanotech Platform

Business Wire: January 19, 2017 – MAASTRICHT, The Netherlands – Cristal Therapeutics, a privately held life sciences company developing novel nanomedicines against cancer and other diseases, today announced the closing of a  $\in 12.8$  million financing round. The financing comes from a consortium headed by Dutch oncology investor Aglaia BioMedical Ventures and Belgian DROIA Oncology Ventures and was complemented by BOM, LIOF, and LBDF. Existing shareholders (founders, Chemelot Ventures, BioGeneration Ventures, Utrecht University Holding, Nedermaas Hightech Ventures) also participated in the round. The new funding will be used to continue and accelerate the clinical development of Cristal Therapeutics' lead candidate CriPec<sup>®</sup> docetaxel, by executing a clinical phase Ib trial, building the momentum for a clinical phase II trial starting later this year. Funds also allow for intensified development of Cristal's nanotech platform for its innovative CriPec<sup>®</sup> DUO and CriPec<sup>®</sup> oligonucleotides programs.

CriPec<sup>®</sup> docetaxel is Cristal Therapeutics' lead candidate in development and represents a novel treatment approach of solid tumours. CriPec<sup>®</sup> nanoparticles with the anticancer drug docetaxel entrapped accumulate in tumour tissue and yield a significantly higher exposure within the tumour, thereby overcoming drawbacks of conventional docetaxel therapies. CriPec<sup>®</sup> docetaxel successfully passed various preclinical studies, demonstrating a significantly enhanced efficacy and an improved safety and tolerability profile. The candidate also successfully passed a clinical phase Ia trial in patients suffering from solid tumours where human tolerability and pharmacokinetics were assessed. Further safety and signs of efficacy will be evaluated in a clinical phase Ib study aiming to confirm the recommended phase II dose level and regimen. CriPec<sup>®</sup> docetaxel is expected to have substantial medical and commercial advantages particularly in combination therapies.

Cristal Therapeutics is continuously searching to broaden the application of its nanomedicine platform. The CriPec<sup>®</sup> DUO concept aims to achieve a synergistic therapeutic response of two anticancer drugs entrapped in one nanoparticle.

Cristal Therapeutics also applies its CriPec<sup>®</sup> platform for the delivery of oligonucleotides to intracellular targets. CriPec's underlying proprietary polymer and linker technology offers exciting perspectives to overcome some of the major hurdles in the oligonucleotide field.

Dr. Joost Holthuis, CEO of Cristal Therapeutics, comments on the new financing round: "We are thrilled to welcome high quality investors Aglaia and DROIA to Cristal Therapeutics, but also BOM, LIOF, and LBDF complementing our group of investors. This clearly represents a growing commitment to nanomedicines and reflects the potential of our drug programs on the basis of the CriPec° technology."

"This funding comes at a time when we are taking meaningful steps forward with our clinical lead candidate CriPec<sup>®</sup> docetaxel towards achieving a better treatment for patients with advanced solid tumours. Today's financing allows us to cover both the upcoming clinical phase Ib and IIa trial with CriPec<sup>®</sup> docetaxel and the preclinical studies for CriPec<sup>®</sup> DUO and CriPec<sup>®</sup> oligonucleotides for the period until 2019."

Mark Krul, partner at Aglaia BioMedical Ventures, says. "Many cancer drugs could become more effective as a result of improved delivery of the compounds to the right cell type and cell compartment. We believe that Cristal Therapeutics' state-of-art and highly versatile drug delivery platform has breakthrough potential in fields where drug delivery remains a key problem, such as for nucleic acid based compounds and immuno-oncology complexes."

Janwillem Naesens, partner at DROIA Oncology Ventures, comments on their investment: "We were impressed by the highly customizable pharmacological properties of Cristal Therapeutics' CriPec<sup>®</sup> nanoparticles, which should enable a broad array of therapeutic applications. The delivery platform clearly stands out amongst other next-generation nanoparticles under development. With the backing of this solid investor base, the seasoned team will be able to explore the full potential of its technology."

The Dutch venture capital firm Aglaia—through its Oncology Funds I and II—invests in groundbreaking technologies that have the potential to translate into solutions for the prevention and treatment of cancer. Aglaia is actively involved in the companies it invests in and works closely with scientists and management teams in the early stages of technological development. By translating high-potential research into commercially and clinically successful products, Aglaia gives meaning to the concept of impact investing, combining financial and social returns. www.aglaia-biomedical.com

DROIA is a venture capital investor focusing exclusively on oncology therapeutics. Operating from Luxembourg and Belgium, DROIA invests worldwide in early-stage drug development companies that apply novel science and innovative approaches to bring highly promising drug candidates to patients. Through its experienced team of in-house scientists and drug developers, DROIA also supports young companies on scientific and development matters. Funded by private investors, DROIA is dedicated to making a difference in the fight against cancer.

Cristal Therapeutics, based in Maastricht, the Netherlands focuses on the development of nanomedicines with improved therapeutic efficacy against cancer and other diseases, such as chronic inflammatory disorders, by using its patented CriPec<sup>®</sup> technology. This technology entraps existing and new drugs in polymer nanoparticles of less than 0.0001 mm diameter. These nanoparticles provide better distribution throughout the body and a more selective release of the drugs at the desired site, such as anticancer drugs that are preferentially targeted to tumours. Therefore, products based on CriPec<sup>®</sup> may provide enhanced efficacy and fewer side effects, thus offering improved disease treatment.

CriPec<sup>®</sup> docetaxel is Cristal Therapeutics' lead candidate in development and represents a novel treatment approach of solid tumours. CriPec<sup>®</sup> docetaxel successfully passed various preclinical studies, demonstrating a significantly enhanced efficacy and an improved safety and tolerability profile. The candidate also successfully passed a clinical phase Ia trial in patients suffering from solid tumours where human tolerability and pharmacokinetics were assessed. In a clinical phase Ib study further safety and signs of efficacy will be evaluated aiming to confirm the recommended phase II dose level and regimen. Later this year, Cristal Therapeutics will start a large clinical phase II study.

CriPec<sup>®</sup> allows for the entrapment of multiple compounds (e.g., two compounds attacking the tumour through different pathways and with different toxicity) in a single nanoparticle, in a well-defined ratio and each with its individual release kinetics, with the aim to generate synergistic efficacy at an acceptable tolerability profile. To boost the selectivity, these CriPec<sup>®</sup> nanoparticles may be actively targeted to the tissue of interest.

The use of oligonucleotides as drugs is receiving a growing interest of pharmaceutical and biotech companies. Worldwide about 150 companies are working on the development of oligonucleotides, but they are all encountering similar delivery problems.

CriPec's underlying proprietary polymer and linker technology offers exciting perspectives to overcome some of the major hurdles in the oligonucleotide field.

In December 2016, Cristal announced a partnership with Belgian biotech iTeos Therapeutics for the development of immunooncology therapeutic candidates by combining CriPec<sup>®</sup> nanoparticles with iTeos small molecule immunomodulators with the aim of optimizing the delivery of those drug candidates into the tumour microenvironment.

### Medical Marijuana, Inc., Investment AXIM<sup>®</sup> Biotech Enters IBS Clinical Trial with CBD Chewing Gum

PRNewswire: January 19, 2017 – SAN DIEGO, CA, U.S.A. – Medical Marijuana, Inc. (OTC: MJNA), the first-ever publicly traded cannabis company in the United States, announced today that its major investment company AXIM® Biotechnologies, Inc. (AXIM® Biotech) (OTC: AXIM) has entered clinical trials at Wageningen University in the Netherlands for treatment of irritable bowel syndrome (IBS) with AXIM's CanChew Plus® cannabidiol (CBD) gum. IBS is the most common disorder diagnosed by gastroenterologists and accounts for up to 12% of total visits to primary care providers, accumulating between 2.4 and 3.5 million annual physician visits for the disease in the United States.

AXIM recently announced that the company had received approval from the Medical Ethical Committee (METC) at Wageningen University for the trial using controlled-release hemp oil CBD chewing gum with patients suffering from IBS. The gum as well as matching placebo gums will be given to trial participants. AXIM will use gum containing 50 mg of CBD per serving during the trial and patients will be allowed up to six chewing gums a day to control their stomach cramps, bloating, pain, and other symptoms. The trial will study the outcome of pain reduction in patients taking the gum containing CBD versus the placebo and record general relief and change in stool frequency.

"We are excited to see that AXIM has reached another milestone in its clinical development program," said Dr. Stuart Titus, CEO of Medical Marijuana, Inc. "IBS is one of the most common disorders in the world, affecting up to 15% of the global population, with no real treatment options available. This is the first advancement in cannabinoid research for treatment of IBS in medical history and gives a clear example of how far ahead AXIM is in its clinical development programs."

"With 35 to 40% of individuals who report IBS in the community being male and between 60 and 65% being female, the cost to society in terms of direct medical expenses and indirect costs associated with loss of productivity and work absenteeism tied to IBS is considerable, estimated from \$21 billion or more," added Dr. Titus.

The trial will include a group of 40 patients, age 18–65, diagnosed with IBS according to ROME III criteria to determine the effectiveness of CanChew Plus<sup>®</sup> in alleviating IBS symptoms.

With positive outcome from the IBS clinical trial, AXIM will be ready to proceed immediately with further trials on its pharmaceutical grade CanChew Rx<sup>™</sup> products for treatment of inflammatory bowel disease (IBD), ulcerative colitis, and Crohn's disease. Wageningen University is a world-class education and research institute in the field of life sciences, agricultural and environmental science, and the only university in the Netherlands to focus on the theme of "healthy food and living environment." According to the Times Higher Education World University Rankings, Wageningen is the best university in the Netherlands and number 1 worldwide in agriculture and forestry for 2016 on the QS World University Rankings.

AXIM<sup>®</sup> Biotechnologies, Inc. (OTC: AXIM) focuses on the research, development, and production of cannabis-based pharmaceutical, nutraceutical, and cosmetic products. Our flagship products include CanChew<sup>®</sup>, a CBD-based controlled release chewing gum, and MedChew Rx, a combination CBD/THC gum that is undergoing clinical trials for the treatment of pain and spasticity associated with multiple sclerosis. We prioritize the well-being of our customers while embracing a solid fiscal strategy. Medical Marijuana, Inc., is a major investor in AXIM. For more information, visit www.AXIMBiotech.com. For details on Medical Marijuana, Inc.'s portfolio and investment companies, visit www.medicalmarijuanainc.com.

## Heron Announces Submission of CINVANTI™ NDA for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV)

Business Wire: January 12, 2017 – SAN DIEGO, CA, U.S.A. – Heron Therapeutics, Inc. (NASDAQ: HRTX), a commercial-stage biotechnology company focused on developing novel best-in-class treatment solutions to address some of the biggest unmet patient needs, today announced submission of the New Drug Application (NDA) for CINVANTI (HTX-019), the first polysorbate 80-free, intravenous formulation of aprepitant for the prevention of CINV, to the U.S. Food and Drug Administration (FDA). Aprepitant belongs to a class of agents known as NK1 receptor antagonists, which are often used in combination with 5-HT3 receptor antagonists for the prevention of CINV.

The NDA filing includes data demonstrating the bioequivalence of CINVANTI to EMEND IV<sup>®</sup> (fosaprepitant), supporting its efficacy for the prevention of both acute and delayed CINV with both moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC). Results also showed CINVANTI was better tolerated than EMEND IV, with significantly fewer adverse events reported with CINVANTI.

"The filing of the NDA for CINVANTI is an important milestone, bringing us one step closer to a new NK1 receptor antagonist treatment option for cancer patients suffering from the debilitating side effects of chemotherapy," said Kimberly J. Manhard, executive vice president, drug development at Heron Therapeutics. "We look forward to working closely with the FDA during the review of the NDA for CINVANTI in anticipation of FDA approval in late 2017."

"CINVANTI is based on the most widely used NK1 receptor antagonist, with almost nine years of safety and efficacy experience," said Barry D. Quart, Pharm.D., chief executive officer of Heron Therapeutics. "Since NK1 receptor antagonists are used in combination with 5-HT3 receptor antagonists, CINVANTI offers a strong strategic and operational fit with Heron's existing commercial product, SUSTOL", our extended-release, injectable product that incorporates the 5-HT3 receptor antagonist granisetron and is also indicated for the prevention of CINV."

CINVANTI is a proprietary intravenous formulation of aprepitant, a NK1 receptor antagonist for the prevention of CINV. NK1 receptor antagonists are typically used in combination with 5-HT3 receptor antagonists. Currently, the only injectable NK1 receptor antagonist approved in the United States contains polysorbate 80, a surfactant, which may cause hypersensitivity reactions, infusion site reactions, or other adverse reactions in some patients. Heron's formulation for CINVANTI does not contain polysorbate 80 and may have a lower incidence of certain types of adverse reactions than reported with the other commercially available injectable NK1 receptor antagonist.

SUSTOL is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens. SUSTOL is an extended-release, injectable 5-HT3 receptor antagonist that utilizes Heron's Biochronomer<sup>®</sup> polymer-based drug delivery technology to maintain therapeutic levels of granisetron for  $\geq$ 5 days. The SUSTOL global phase 3 development program was comprised of two large, guideline-based clinical trials that evaluated efficacy and safety in more than 2,000 patients with cancer. The efficacy of SUSTOL in preventing nausea and vomiting was evaluated in both the acute phase (day 1 following chemotherapy) and the delayed phase (days 2–5 following chemotherapy). Please see full prescribing information, including additional important safety information, available at www.SUSTOL.com.

Heron Therapeutics, Inc., is a commercial-stage biotechnology company focused on improving the lives of patients by developing best-in-class medicines that address major unmet medical needs. Heron is developing novel, patient-focused solutions that apply its innovative science and technologies to already-approved pharmacological agents for patients suffering from cancer or pain. For more information, visit www.herontx.com.

### ForSight VISION4, Inc., Announces Acquisition by Roche

PRNewswire: January 10, 2017 – MENLO PARK, CA, U.S.A. – ForSight VISION4, a privately held biotechnology company revolutionizing drug delivery for treatment of retinal diseases, announced today that it has been acquired by Roche Holdings Inc. The company is the fourth venture created by the Menlo Park incubator, ForSight Labs, LLC, and was funded entirely by two of the leading venture capital firms in Silicon Valley, Morgenthaler Ventures and Versant Ventures.

The acquisition expands Roche's exclusive access to the ForSight VISION4 PDS technology for long-acting delivery of therapeutics to the eye. In 2010, ForSight VISION4, Inc., announced a collaboration and license agreement with Genentech, a member of the Roche Group, for exclusive rights to use ForSight VISION4's proprietary drug delivery technology for the target VEGF-A.

"This transaction marks the successful culmination of an early and ongoing collaboration between the ForSight VISION4 team and the team at Genentech, and puts the PDS technology on a path to revolutionize retinal therapies for patients worldwide," said K. Angela Macfarlane, president and CEO of ForSight VISION4, Inc. "We believe that Roche, a leader in ophthalmic drug development, is the ideal partner to drive the further development of the PDS."

The PDS is a durable intravitreal implant that is placed through a scleral incision in a one-time surgical procedure. It is then refilled using a proprietary refill needle by a physician in an office setting. The ranibizumab PDS is currently in a phase II study, the "LADDER" Study (NCT02510794) sponsored by Genentech to define the duration of drug delivery possible with the PDS technology.

ForSight VISION4 has developed the PDS to facilitate a wide array of molecules and therapeutic payloads, including delivery of small molecules that typically have a short retention time inside the eye. The acquisition by Roche provides the opportunity for the PDS technology to be applied broadly to other molecules in the Roche pipeline as an approach for extending the duration between treatments for intravitreally injected drugs.

Retinal vascular diseases, such as neovascular age-related macular degeneration and diabetic eye disease, are leading causes of vision loss in both working-aged and elderly people. Today, the most common treatment for these sight-threatening diseases is intraocular injections of Anti-VEGF drugs. The intensity of treatment can place a burden on patients, their caregivers, and physicians, and recent studies have shown that under-treatment may lead to significant, unrecoverable vision loss. Technologies that could extend the duration between treatments could offer a significant benefit to patients by reducing the burden of treatment and leading to better vision outcomes.

"In 2005, I witnessed the presentation at the American Society of Retina Specialists meeting of the dramatic visual improvements from monthly injections of LUCENTIS for choroidal neovascularization associated with AMD, which profoundly changed ophthalmology," commented Eugene De Juan, Jr., MD, founder of ForSight VISION4, Inc. "The ForSight VISION4 PDS was developed specifically to continue to enhance the treatment of patients with retinal diseases. I am very appreciative that Roche is again leading the way to improving these patients' lives."

ForSight Labs, LLC (www.forsightlabs.com) is an ophthalmic incubator established in 2005 by renowned ophthalmologist and retinal surgeon Eugene de Juan, Jr., M.D., in collaboration with The Foundry (www.thefoundry.com). Over the past 10 years, ForSight Labs has started five additional VISION companies, which have collectively raised over \$150M in capital: Transcend Medical, Inc. (Acquired by ALCON), ForSight Newco II, Inc. (Acquired by QLT), NEXIS Vision, Inc. (Out-Licensed), ForSight VISION5, Inc. (Acquired by Allergan), and ForSight VISION6, Inc., including subsidiary FSV6, Ltd., Israel (privately held).

### IACTA Pharmaceuticals Licenses NM133 from Nanomerics for Treatment of Dry Eye

Business Wire: January 10, 2017 – NEWPORT BEACH, CA, U.S.A. – IACTA Pharmaceuticals, Inc., a privately held pharmaceutical company, has acquired the North American rights to develop and commercialize NM133, an investigational medicine designed to help treat dry eye, from its developer, Nanomerics, Ltd.

Nanomerics is a privately held, U.K.-based, research-stage company with a proprietary molecular envelope technology (MET) licensed from University College London that allows a hydrophobic drug such as cyclosporine to be encapsulated and delivered to the tissues of the eye.

Damon Burrows, founder and CEO of IACTA Pharmaceuticals, said, "We are enthusiastic about partnering with Nanomerics and are grateful that they have placed their trust in us as their North American licensee. We strongly believe in the promise of MET technology for the treatment of a range of conditions including dry eye."

Prof. Andreas Schatzlein, CEO of Nanomerics, said, "Nanomerics believes IACTA is the ideal North American licensee for NM133. The need for better medicines remains undiminished and drugs need to be used to their full potential to deliver patient benefit. Nanomerics' molecular envelope technology (MET) is engineered at the nanoscale to efficiently deliver drugs for a variety of applications. NM133 is a product in which many of the MET attributes are being exploited to bring tangible benefits to those suffering from dry eye disease."

Molecular envelope technology (MET) nanoparticles are engineered from biocompatible polymers. MET particles are engineered by creating amphiphilic polymers that can self-assemble into micelles. Hydrophobic drugs can be encapsulated into these micelles with high efficacy and are accommodated in the hydrophobic nanodomains. The MET nanoparticles are stable and small (approx. 50 nm). Molecular dynamics simulations demonstrate that the material is encapsulated in a very dynamic fashion, which facilitates drug release across barriers.

NM133 is a nano enabled form of cyclosporine A that is being investigated for the treatment of dry eye. Cyclosporine A is an immunosuppressant that helps tear secretion and improve tear film stability which improves the symptoms of dry eye syndrome patients. (Mantelli, F, Massaro-Giordano, M, Macchi, I, Lambiase, A, Bonini, S. The cellular mechanisms of dry eye: From pathogenesis to treatment. J Cell Physiol. 2013; 228(12): 2253-2256.) However, regardless of cyclosporine A's benefits, it is an extremely hydrophobic drug. Hydrophobic means it "hates water" and simply does not mix with water. For that reason, ophthalmic formulations of cyclosporine typically rely on an oil-in-water emulsion for drug delivery into the tissues of the eye. NM133 offers a completely new approach to the delivery of cyclosporine A. Using the patent-protected MET, NM133 effectively wraps and solubilizes cyclosporine A in a protective cover, helping it across the epithelial barriers of the eye.

IACTA Pharmaceuticals, located in Newport Beach, California, is a privately held company focused on bringing the latest technology to the healthcare industry and eyecare specifically. For more information, visit iactapharma.com.

Nanomerics is a specialty pharmaceutical company focused on the development of pharmaceutical products with enhanced bioavailability. The company uses proprietary pharmaceutical nanotechnology and knowhow developed by the founding scientists Prof. Ijeoma F. Uchegbu and Prof. Andreas G. Schätzlein at the Universities of Strathclyde and Glasgow and, latterly, at the UCL School of Pharmacy. The company's MET technology delivers a step change in target tissue availability of drugs and biological APIs such as peptides across a number of epithelial barriers. Nanomerics exploits its knowhow and technology to develop its product pipeline of new therapeutic entities (NTEs) and NCEs.

## Hammock Pharmaceuticals Announces the Licensing of Women's Health and Urological Technology Platform from MilanaPharm

PRNewswire: January 9, 2017 – CHARLOTTE, NC, U.S.A. – Hammock Pharmaceuticals, Inc., today announced the execution of a license agreement with MilanaPharm/TriLogic Pharma for the exclusive global rights to their women's health and urology hydrogel technology platform. This novel technology is a bioadhesive copolymer that allows for *in situ* gelation that transforms a liquid into a gel at body temperature. Patents have been granted in the United States, European Union, and China, with additional patents pending that would grant exclusivity through 2035.

Hammock's lead products are metronidazole and clindamycin vaginal gel for the treatment of bacterial vaginosis (BV). Over 21 million women in the United States experience episodes of BV with many treated by intravaginal products. In a pilot study, Hammock's product showed an 88% cure rate, which would be a significant improvement over currently marketed intravaginal BV therapies. The company expects to initiate a phase III clinical program in the second half of 2017. In addition, Hammock anticipates executing licensing agreements for ex-U.S. rights in 2017.

Hammock's lead urology product, HPI-1216, is being developed for the treatment of radiation cystitis, a common side effect from pelvic radiation treatment for pelvic tumors. Cystitis is a painful bladder condition that is extremely disruptive to the lives of radiation patients. Hammock expects to initiate late stage trials by the end of 2017.

"I am delighted to announce that we have officially launched Hammock Pharmaceuticals, a company committed to the development and commercialization of novel, valuable products in women's health and urology," commented William R. Maichle, CEO of Hammock Pharma. "We congratulate our team, shareholders, MilanaPharm, and TriLogic on this transaction and look forward to enhancing Hammock's value through execution of our development programs and commercial stage acquisitions. We also are excited about the opportunity to use this novel technology to develop additional late stage compounds."

Jim Harwick, president of MilanaPharm, said, "We are excited to partner with Hammock Pharmaceuticals on the development of new applications for women's health and urology. We continue to be pleased with the versatility of the hydrogel technology and the wide range of therapeutic classes and actives that can be developed with our novel drug delivery platform."

Hammock Pharmaceuticals is an emerging branded, specialty pharmaceutical company focused on the development and commercialization of women's health and urology products. We pride ourselves on innovation, respect, and exceptional service for all of our stakeholders. Hammock's management has over 80 years of healthcare experience and is based in Charlotte, North Carolina. For more information, visit www.hammockpharma.com.

MilanaPharm is a specialty pharmaceutical company built upon a proprietary drug delivery platform for numerous active compounds. The hydrogel platform, TRI-726, is capable of delivering actives over several hours to several days. Our immediate focus is in chronic wound management with effective alternatives for healing and pain. MilanaPharm is based in Tallassee, Alabama. For more information, visit www.milanapharm.com.

### Ascendia Pharmaceuticals Announces Issuance of a New Patent on Its ASD-002 Program for Acute Coronary Syndrome

Business Wire: January 6, 2017 – NORTH BRUNSWICK, NJ, U.S.A. – Ascendia Pharmaceuticals, a specialty pharmaceutical company engaged in nano-formulation design, development, and manufacture for poorly soluble molecules, today announced that it has been awarded a new patent. U.S. patent number 9,480,680, entitled "Stable Pharmaceutical Composition of Clopidogrel Free Base for Oral and Parenteral Delivery," describes the application of Ascendia's EmulSol nanotechnology to formulate a stable, ready-to-use, rapid-onset, injectable form of clopidogrel.

Clopidogrel, a top-selling blood thinner medicine, has never been successfully developed in an injectable dosage form due to its inherent chemical instability and poor solubility. "There is a significant unmet medical need for a parenteral clopidogrel dosage form for the treatment of acute coronary syndrome under life-threatening situations," said Jingjun "Jim" Huang, Ph.D., CEO of Ascendia.

"With our nanoemulsion platform technology, Ascendia has demonstrated that a ready-to-use, stable and soluble, parenteral form of clopidogrel is both technically and commercially feasible." When a patient presents with a suspected coronary event, a high oral dose of clopidogrel is frequently administered as the only available forms of clopidogrel are tablets—not ideal in an emergency setting. Also, when delivered orally, there is a significant delay in the time required for the medicine to become fully absorbed and effective.

ASD-002 can be administered as a single high-dose injection of clopidogrel, capable of overcoming CYP2C19 resistance in a percutaneous coronary intervention (PCI) setting (which 30% of patients experience). Thus ASD-002 will address the unmet need for rapid platelet inhibition, while reducing bleeding risk, associated with newer P2Y12 agents, and has the potential to expand the \$2 billion PCI market in peripheral artery disease. ASD-002 for injection also has the potential to provide an advantage compared to the recently approved IV antithrombotic drug cangrelor, as ASD-002 should not have an indication exclusion for patients currently on a P2Y12 inhibitor.

Ascendia is a specialty pharmaceutical company dedicated to developing enhanced formulations of existing drug products, and enabling formulations for preclinical and clinical stage drug candidates. We specialize in creating formulation solutions for poorly water-soluble molecules and other challenging pharmaceutical development projects. Ascendia formulates products for injection (IV, SC, or IM); transdermal, ophthalmic or nasal delivery; and both immediate-release and controlled-release products for oral administration. We have three technology platforms—EmulSol for producing nano-emulsions, AmorSol for creating amorphous solid dispersions, and NanoSol for formulating nano-particles. For more information, please visit Ascendia's website at www.ascendiapharma.com.

### TARIS Biomedical<sup>®</sup> Announces Positive Results from Phase 1b Trial of TAR-200 (GemRIS™) in Patients with Muscle Invasive Bladder Cancer

Business Wire: January 6, 2017 – LEXINGTON, MA, U.S.A. – TARIS Biomedical LLC, a company developing targeted new treatments for millions of patients suffering from difficult-to-treat bladder diseases, announced today that it has closed initial enrollment in its phase 1b clinical trial of TAR-200 (GemRIS<sup>™</sup>) following highly positive results. TAR-200, a drug-device combination product utilizing the TARIS<sup>®</sup> system, is designed to release gemcitabine continuously into the bladder over seven days. This open-label study assessed the safety and tolerability of TAR-200 when used in patients with MIBC following initial diagnosis and prior to radical cystectomy. In addition, the study evaluated antitumor activity at day 28 of the study. The treatment regimen employed in this study included two system deployments separated by a 14-day rest period.

Preliminary results indicate that the system was well tolerated over two seven-day treatment periods, with no local or systemic tolerability findings. To be eligible for enrollment, patients were required to have visible bulky residual tumor of at least 3 cm in size, clinical stage T2 or T3. Striking tumor responses, including complete tumor ablation or substantial shrinkage, were observed visually at the time of cystectomy in 8 of 10 patients. While the study was originally designed to include up to 20 subjects, the company closed enrollment early following these positive results in order to accelerate the clinical advancement of TAR-200. The company expects complete data from this study, including histopathological assessment, to be presented at a major upcoming medical meeting.

"The results of this study are very exciting," said Siamak Daneshmand, M.D., associate professor of urology, University of Southern California, and principal investigator for the TAR-200-101 study. "TAR-200 appears to be remarkably well-tolerated in patients who have recently undergone extensive transurethral resection of the bladder. Moreover, the unexpected activity observed in these heavily diseased subjects in just 28 days indicates the significant potential of this product in a broad population of patients with MIBC, often a very difficult disease to treat."

"TARIS is extremely excited about the compelling results from this study and plans to rapidly advance the product into later-stage clinical trials in bladder cancer in 2017," said Purnanand Sarma, Ph.D., president and CEO of TARIS. "The tumor response we have seen to date suggests TAR-200 may offer a fundamentally new treatment option for patients with MIBC, where the current standard of care includes bladder removal. We share the excitement of the study investigators about the potential impact that TAR-200 may have on the lives of patients across the spectrum of bladder cancer."

The phase 1b open-label study was designed to assess whether continuous local exposure to gemcitabine is safe and tolerable in patients with MIBC. The study was initially designed to enroll up to 20 subjects across three sites in the United States. Enrolled subjects had bulky residual clinical stage T2 or T3b MIBC tumors following initial transurethral resection of bladder tumor (TURBT) and were ineligible to receive cisplatin-based combination neoadjuvant chemotherapy. Subjects received two placements of TAR-200 during days 1–7 and 21–28 in the 28-day window between TURBT and radical cystectomy. Subjects were evaluated for safety, tolerability, and evidence of antitumor effects.

TAR-200 (GemRIS<sup>™</sup>) is TARIS Biomedical's first program in bladder cancer. TAR-200 is a drug-device combination product designed to release gemcitabine continuously into the bladder over seven days. Gemcitabine is commonly used to treat multiple cancers alone and in combination with other chemotherapeutic drugs and is routinely given intravenously. TARIS<sup>®</sup> believes TAR-200 has the potential to set a new standard of care in bladder cancer, with enhanced efficacy and minimal systemic side effects compared to current approaches. TARIS<sup>®</sup> is developing TAR-200 to address unmet needs in both muscle invasive and non-muscle invasive bladder cancer.

The TARIS<sup>®</sup> system is a controlled release dosage form for use in the bladder. The system uses passive delivery principles to continuously release drug in the bladder over weeks to months. It is deployed into and retrieved from the bladder using minimally invasive in-office procedures. This technology allows drug release to be tailored to match the needs of specific treatment regimens.

TARIS Biomedical<sup>®</sup> is building a unique therapeutically focused urology company, developing targeted new treatments for millions of patients suffering from difficult-to-treat bladder diseases. We are advancing therapies for debilitating conditions, including bladder cancer and overactive bladder, enabled by continuous local dosing where it is needed. www.tarisbiomedical.com

# Novaliq Announces Positive Topline Results of Phase 2 Clinical Trial Evaluating CyclASol® in Adults with Moderate to Severe Dry Eye Disease

Business Wire: January 5, 2017 – HEIDELBERG, Germany – Novaliq GmbH, a specialty pharmaceutical company with a disruptive drug delivery platform that transforms poorly soluble drugs into effective therapeutics for ophthalmology, today announced positive phase 2 results evaluating CyclASol<sup>®</sup>, a clear, preservative-free cyclosporine A solution, in 207 patients with moderate to severe dry eye disease (DED). CyclASol showed a consistent reduction in corneal fluorescein staining, the primary sign endpoint, with an early onset of action over the four-month treatment period.

This phase 2 randomized, double-masked, vehicle-controlled, multi-center U.S. study consisted of four treatment groups, including two CyclASol groups (0.05 and 0.1%), an open label active control, and a placebo (vehicle control) group. Both CyclASol groups showed a significant improvement in corneal staining compared with the vehicle over the four-month treatment period. In particular, the central area of the cornea seems to benefit most, which is an important aspect for the visual function in dry eye patients. All treatment groups demonstrated improvement in symptoms, with CyclASol showing improvements over vehicle in subgroups. Data further indicate an early onset of action by reduction in corneal and conjunctival staining in as little as 14 days.

"These phase 2 results are very promising and verify the preclinical data, in particular regarding an improvement in corneal staining and the tendency to an earlier onset of action," said Michael E. Stern, Ph.D. and scientific advisory board member for Novaliq. "The role of cyclosporine A in resolving ocular surface inflammation has been well demonstrated and the novel CyclASol formulation may provide a promising new option for physicians and their patients suffering from moderate to severe dry eye disease."

Both CyclASol concentrations showed excellent safety, tolerability, and comfort profile with 98% of the enrolled patients completing the treatment period. No serious adverse events (SAEs) related to CyclASol were reported.

"Consistent improvements in several measures of ocular inflammation of dry eye disease, particularly the improvement in central corneal staining, is a very important feature of the formulation because it positively influences visual function. This, combined with the early onset of action and an excellent tolerability profile, represents a highly relevant improvement over currently available therapies," said Claus Cursiefen, M.D., Ph.D., FEBO, chairman and professor, Department of Ophthalmology, University of Cologne, and member of Novaliq's scientific advisory board.

"We are excited as these positive results further validate the potential of our EyeSol<sup>®</sup> drug delivery platform," said Christian Roesky, Ph.D. and chief executive officer Novaliq. "There is a high medical need for innovative, effective, fast-acting and safe treatment options for patients with dry eye disease. These encouraging results will guide our further clinical development in this important disease."

CyclASol is a clear, preservative-free ophthalmic solution of cyclosporine A formulated using Novaliq's proprietary EyeSol technology.

Novaliq GmbH, founded in 2007, is a Heidelberg-based specialty pharmaceutical company focused on ophthalmology. Its mission is to transform poorly soluble drugs into effective ocular therapeutics for both the front and the back of the eye. Novaliq's proprietary EyeSol technology enhances the topical bioavailability, stability, and safety of traditionally insoluble or unstable drugs improving the delivery, efficacy, and convenience of treatments for ocular surface diseases including dry eye through preservative free and multidose formulations. Novaliq's most advanced product is NovaTears<sup>®</sup> with CE-marking based on Novaliq's proprietary EyeSol technology. NovaTears is marketed under the brand name EvoTears<sup>®</sup> in Europe. More on www.novaliq.com.

# Researchers at the Gene Editing Institute at Christiana Care Health System Develop New System to Perform Precise "Surgery" on the Human Genome

Christianacare.org: January 4, 2017 – Wilmington, DE, U.S.A. – Molecular biologists at Christiana Care Health System's Gene Editing Institute have developed a new system that allows them to not only repair damaged DNA within human cells but also to determine when the DNA repair machinery has introduced unwanted genetic changes alongside, or instead of, the desired repair.

A team of researchers led by Eric Kmiec, Ph.D., director of the Gene Editing Institute at the Helen F. Graham Cancer and Research Institute at Christiana Care, published its findings using a modified version of the cutting-edge CRISPR/Cas9 gene editing technique in the January 3 issue of the scientific journal *PLOS One*.

The modified CRISPR/Cas9 technique, called excision and corrective therapy, or EXACT, uses a short single-stranded piece of DNA called an oligonucleotide to serve as both a bandage and a template during the repair of a genetic mutation.

"The advancement here is a new concept of using donor DNA as an oligonucleotide to act as a Band-Aid across a gap created by the CRISPR [ribonucleoprotein complex], and then allowing replication to fill in the gap, and then the oligonucleotide dissociates and on you go," said Dr. Kmiec.

The published paper, titled "Insertional Mutagenesis by CRISPR/Cas9 Ribonuclear Gene Editing in Cells Targeted for Point Mutation Repair Directed by Short Single-Stranded DNA Oligonucleotides," describes how the EXACT CRISPR/Cas9 technique can be used to repair what are called point mutations—single changes in the DNA code that can render genes nonfunctional and produce hereditary diseases in humans, such as sickle cell anemia or Gaucher's disease.

The present study follows an earlier report published in the September 9, 2016, issue of the journal *Scientific Reports*, in which Dr. Kmiec and his colleagues established that their EXACT CRISPR/Cas9 gene editing technique functions using the "Band-Aid template" repair mechanism that they had predicted.

In the *PLOS One* paper, Dr. Kmiec and his colleagues report using a single-stranded DNA template with a preassembled CRISPR/ Cas9 ribonucleoprotein complex to fix a point mutation in human cells that have been engineered to express a fluorescent protein only if a single change in the DNA that encodes the fluorescent protein can be repaired.

The researchers report that their EXACT gene editing approach does in fact result in a significant amount of point mutation repair, thereby producing cells that make functional fluorescent protein. More importantly, Dr. Kmiec and his colleagues also characterize undesirable mutations that sometimes occur alongside of or instead of the desirable point mutation repair when using the EXACT CRISPR/Cas9 gene editing system. Dr. Kmiec and his coauthors refer to these undesirable side mutations, in which DNA is inappropriately inserted or deleted, as "collateral damage" or "on-site mutagenesis."

"If you lose DNA, even one or two bases, even if you fix the point-mutation the gene is disabled, because the gene can no longer code for the proper protein," said Dr. Kmiec. "So even though you have successfully corrected the gene, the problem is that you've also introduced some sort of secondary mutation at the site, and that causes the gene to be completely nonfunctional."

As reported by Dr. Kmiec and colleagues, on-site mutagenesis can occur even when repair of the point mutation has not taken place, meaning that CRISPR/Cas9 ribonucleoprotein complexes can produce additional genetic lesions called indels (short for insertions and deletions) at a target site without carrying out the function they were placed there to perform.

In their *PLOS One* paper, the researchers map out exactly where and how indels occur during on-site mutagenesis in greater detail than has been reported previously, examining exactly what happens to both copies of the DNA strand after the CRISPR/Cas9 ribonucleoprotein complex has done its work.

Overcoming the problem of on-site mutagenesis and the genetic scar tissue it leaves behind will be necessary if CRISPR/Cas9mediated gene therapy is to become useful in the clinical setting. As Dr. Kmiec and his colleagues suggest, solving this problem will not be easy, as the DNA-repair machinery that cells use to perform point mutation repairs is inherently error prone.

Based on the greater mechanistic understanding provided by his recent studies, Dr. Kmiec says he remains optimistic that on-site mutagenesis is a problem that can be overcome.

"We are more optimistic now, seeing this data, that we will be able to fix point mutations efficiently, using this mechanism as opposed to other things that are now being reported in the literature," Dr. Kmiec said. "It's an advance that I think will give people hope that these kind of point mutations can be fixed if we use the proper tools to fix them."

In order to take his CRISPR/Cas9 system into the clinical setting, Dr. Kmiec says it will be necessary to further stabilize the repair complex at the site of the mutation, which should cut down on the occurrence of on-site mutagenesis.

Dr. Kmiec likens the repair process to the way in which a bandage can facilitate wound healing, noting that wounds "heal a lot faster if the bandage stays in place a lot longer. So the more times you wrap it with tape, or in this case, the more stable the binding, the more efficient the point mutation repair is going to be."

To be effective in the clinical setting, Dr. Kmiec and his colleagues also must figure out how to get the CRISPR/Cas9 machinery into the progenitor cells that give rise to mature, therapeutically relevant cells in the body. Dr. Kmiec says this is an active area of research for his laboratory.

Despite all of these challenges, Dr. Kmiec hopes that CRISPR/Cas9 gene therapy with EXACT could be in human clinical trials at Christiana Care within 18 to 24 months.

Dr. Kmiec says he feels confident that clinical trials will be forthcoming in large part because of the ease with which he can collaborate with his clinically oriented colleagues within the Christiana Care Health System. "Christiana Care is such a great, fully integrated hospital complex," he said. "I can walk down the hall and talk to the head of hematology here."

Notably, Christiana Care's Gene Editing Institute also recently entered into a partnership with the Wistar Institute in Philadelphia, with a goal of further accelerating research into repairing damage to the human genome.

Dr. Kmiec's colleagues who contributed to the *PLOS One* paper as authors included Pawel Bialk at the Gene Editing Institute, Natalia Rivera-Torres and Kelly Banas at the University of Delaware Department of Medical Laboratory Science, and Kevin Bloh at the Nemours Center for Childhood Cancer Research.

The Gene Editing Institute at the Graham Cancer Center is a worldwide leader in personalized genetic medicine. Founded and led by Dr. Kmiec, 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. The Gene Editing Institute also provides instruction in the design and implementation of these precise new genetic tools.

The Helen F. Graham Cancer Center and Research Institute, a National Cancer Institute Community Oncology Research Program, is part of Christiana Care Health System. With more than 220,000 patient visits last year, the Graham Cancer Center is recognized as a national model for multidisciplinary cancer care and a top enroller in U.S. clinical research trials.

### December

### Tokai Pharmaceuticals and Otic Pharma Enter into Share Purchase Agreement

Business Wire: December 22, 2016 – BOSTON, MA, and IRVINE, CA, U.S.A., and REHOVOT, Israel – Tokai Pharmaceuticals Inc. (NASDAQ: TKAI) and Otic Pharma Ltd., a privately held, clinical-stage pharmaceutical company focusing on the development and commercialization of products for disorders of the ear, nose, and throat (ENT), today announced that the two companies, together with the shareholders of Otic Pharma, have entered into a definitive share purchase agreement under which the shareholders of Otic Pharma will become the majority owners of Tokai.

The transaction will result in a NASDAQ-listed company focused on the development and commercialization of products for ENT disorders, including Otic Pharma's lead candidate which is a nasally administered, combination drug product (OP-02) intended to address the underlying cause of otitis media and Eustachian tube dysfunction (OM/ETD), a condition that affects more than 700 million people around the world every year. The company will operate under the name OticPharma, Inc., and will be led by Gregory J. Flesher, current chief executive officer of Otic Pharma Ltd. Current president and chief executive officer of Tokai, Jodie Morrison, will remain as a member of the board of directors.

"Over the last several months, Tokai has conducted an extensive review of strategic alternatives aimed at maximizing value for our shareholders over the long-term," said Jodie Morrison, president and CEO of Tokai Pharmaceuticals. "We believe the proposed

transaction with Otic Pharma, a company that has both a promising pipeline and an experienced leadership team with a track record of creating significant shareholder value in public pharmaceutical companies, advances this goal."

"Our lead program in otitis media, OP-02, has significant potential," said Gregory J. Flesher, chief executive officer of Otic Pharma. "OP-02 is an investigational drug product designed to break the cycle of recurrent and chronic otitis media which affect millions of people around the world. We expect to have phase 1 clinical pharmacodynamic data in the first half of 2017 and, with this transaction, to have the capital needed to be able to move directly into phase 2 development to explore the product's ability to prevent otitis media in children."

Upon the close of the proposed transaction, the board of directors of the combined company will consist of seven members, three to be designated by Tokai and four to be designated by Otic Pharma. Officers of the new company will be Gregory J. Flesher, president and chief executive officer; Christine G. Ocampo, chief financial and compliance officer; and Dr. Catherine C. Turkel, chief development officer.

An Otic Pharma investor syndicate, including current shareholders and members of the management team, has committed to invest \$7 million of additional capital in connection with the share purchase agreement.

Otic Pharma is a clinical-stage pharmaceutical company focusing on the development and commercialization of products for disorders of the ear, nose, and throat (ENT). The company has two platform technologies, each of which has the potential to be developed for multiple ENT indications. The company is currently developing a nasally administered, combination drug product (OP-02) intended to address the underlying cause of otitis media and Eustachian tube dysfunction (OM/ETD), a condition that affects more than 700 million people around the world every year. Otitis media is one of the most common diseases seen in pediatric practice and the most frequent reason children consume antibiotics or undergo surgery. The company also has a foam-based drug delivery technology platform (OP-01) that can be used to deliver drugs into the ear, nose, and sinus cavities. The company is currently developing OP-01 as an improved treatment option for acute otitis externa ("swimmers ear"). For more information on the company, please visit www.oticpharma.com.

Tokai Pharmaceuticals is a biopharmaceutical company previously focused on developing and commercializing innovative therapies for prostate cancer and other hormonally driven diseases. The ARMOR2 and ARMOR3-SV clinical trials of Tokai's drug candidate, galeterone, for the treatment of metastatic castration-resistant prostate cancer (mCRPC) have been closed, with only patients in ARMOR2 long-term extension continuing treatment at this time. Plans remain in effect to present data from the ARMOR3-SV trial in a scientific forum once fully available and analyzed. Assessment of plans for galeterone, the ARDA platform, and Tokai's AR-V7 assay work are underway at this time.

## Innovus Pharma Strengthens Its Respiratory Franchise with the In-Licensing of Lertal<sup>®</sup> Tablets, a Clinically Proven Supplement for the Relief of Allergic Rhinitis Symptoms from NTC for the United States and Canada

Business Wire: December 19, 2016 – SAN DIEGO, CA, U.S.A. – Innovus Pharmaceuticals, Inc. ("Innovus Pharma") (OTCQB Venture Market: INNV), an emerging commercial-stage pharmaceutical company that delivers safe, innovative, and effective over-thecounter medicine and consumer care products to improve men's and women's health and respiratory diseases, today announced the inlicensing of Lertal<sup>®</sup> tablets for the management of allergic rhinitis from NTC S.r.l. ("NTC"), an Italian company, for sale by Innovus Pharma in the United States and Canada. Under the terms of the exclusive license agreement, Innovus Pharma agreed to pay an upfront payment, transfer price, and sales milestones during the term of the agreement.

"Strengthening our respiratory franchise is an important goal for us and adding more products such as Lertal<sup>®</sup> as a cross sell or potentially in a kit format with FlutiCare<sup>™</sup>, when that product is eventually approved by the FDA, will give Innovus Pharma an immense advantage over our competitors," said Innovus Pharma chief executive officer Dr. Bassam Damaj. "We continue to look at other respiratory products to in-license to further build out our respiratory franchise."

"We are proud to be partnering with Innovus Pharma in the United States and Canada so Lertal<sup>®</sup> will be available to patients who regularly suffer from allergy symptoms," said Dr. Riccardo Carbucicchio, chief executive officer of NTC. "Innovus Pharma was positively impressed with our promising clinical trial results of Lertal<sup>®</sup>, which saw reductions in both nasal and ocular symptoms in allergic patients. In view of these results, we are now supporting another larger randomized, multicenter, placebo controlled study in perennial and seasonal allergy in pediatric patients. Lertal<sup>®</sup> is meant to contribute to a reduction in daily consumption of antiallergic drugs."

Lertal<sup>®</sup> is a patented formulation produced in bilayer tablets with a technology that allows a controlled release of the ingredients. The fast-release layer allows the rapid antihistaminic activity of perilla. The sustained-release layer enhances quercetin and vitamin D3 bioavailability, thanks to its lipidic matrix, and exerts antiallergic activity spread over time.

Lertal<sup>®</sup> was studied in a clinical trial assessing the reduction of both nasal and ocular symptoms in allergic patients, and daily consumption of antiallergic drugs, over a period of 30 days. Lertal<sup>®</sup> showed a reduction of approximately 70% in total symptom scores and a reduction of approximately 73% in the use of antiallergic drugs. There were no side effects noted during the administration of Lertal<sup>®</sup>, and all the patients enrolled finished the study with good compliance.

The World Health Organization ("WHO") classifies allergies as the fourth most important chronic disease in the world. Allergic rhinitis ("AR") is the most common form of noninfectious rhinitis, affecting between 10 and 30% of all adults in the United States and as many as 40% of U.S. children. Epidemiologic studies show that the prevalence of AR is expected to still be important in the next decades. The World Allergy Organization ("WAO") has estimated that 400 million people in the world suffer from AR, which remains to a large extent underdiagnosed and undertreated.

Headquartered in San Diego, Innovus Pharma is an emerging leader in OTC and consumer products for men's and women's health and respiratory diseases. The company generates revenues from its lead products BTH<sup>®</sup> testosterone booster, BTH<sup>®</sup> human growth agent, Zestra<sup>®</sup> for female arousal, and EjectDelay<sup>®</sup> for premature ejaculation and has an additional five marketed products in this space, including Sensum+<sup>®</sup> for the indication of reduced penile sensitivity, Zestra Glide<sup>®</sup>, Vesele<sup>®</sup> for promoting sexual and cognitive health, Androferti<sup>®</sup> (in the United States and Canada) to support overall male reproductive health and sperm quality, BTH<sup>®</sup> vision formula, BTH<sup>®</sup> Blood Sugar, UriVarx<sup>™</sup> for bladder health, among others, and eventually FlutiCare<sup>™</sup> OTC for allergic rhinitis, if its ANDA is approved by the U.S. FDA. For more information, go to www.innovuspharma.com.

NTC, headquartered in Milan, Italy, is a B2B pharmaceutical company that develops pharmaceutical products, medical devices, and food supplements. NTC distributes its products through third parties in more than 70 countries in the world through a large network of partners. In addition to allergy, NTC is involved in the development of products in ophthalmology, gastroenterology, and women's health. For more information, go to www.ntcpharma.com.

### Ironshore Pharmaceuticals Announces FDA Acceptance of HLD200 New Drug Application for Treatment of ADHD

Business Wire: December 15, 2016 – GEORGE TOWN, Grand Cayman – Ironshore Pharmaceuticals and Development, Inc. ("Ironshore"), a wholly owned subsidiary of Highland Therapeutics Inc., today announced that the U.S. Food and Drug Administration (FDA) has accepted for review the New Drug Application (NDA) for HLD200 (delayed-release and extended-release methylphenidate capsules), which was developed as a potential new option for physicians treating patients with attention-deficit/ hyperactivity disorder (ADHD). HLD200 is the only stimulant medication intended for dosage administration in the evening, prior to bedtime, to target the control of ADHD symptoms and improve functioning from the time the patient awakens and throughout the day. The expected action date by the FDA under the Prescription Drug User Fee Act (PDUFA) is July 30, 2017.

"We are pleased to confirm the progression of HLD200 through the regulatory process at the FDA and look forward to collaborating with the agency in 2017," said Dr. Bev Incledon, executive vice president, research and development. "The NDA filed in support of HLD200 was substantive and included data from two pivotal phase 3 trials, an exploratory phase 3 study, and several pharmacokinetic trials in children, adolescents, and adults. In addition to this rigorous clinical development program, the company also completed several normative studies designed to further validate the Before School Functioning Questionnaire (BSFQ) and the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R) morning (AM) and evening (PM) subscales, which may become important screening and assessment tools in the clinical setting."

HLD200 is the first product that leverages Ironshore's proprietary DELEXIS<sup>®</sup> technology platform, which could have a meaningful impact on health outcomes in a variety of therapeutic areas including, among others, central nervous system disorders and inflammatory bowel disease.

"It is important to recognize that while there are many effective medications for the treatment of ADHD, there still is widespread suffering among a substantial portion of families whose lives are materially and adversely affected. I believe we can improve clinical outcomes by attempting to optimize the delivery of stimulant medications," said Dr. Randy Sallee, chief medical officer. "I would like to thank the patients, parents, clinical investigators, and employees for their enthusiasm, dedication, and perseverance over the eight years of development."

"In addition, based on the positive results from an open-label tolerability study in pediatric patients with ADHD, I am pleased to announce our plans to move HLD100 (a delayed-release and extended-release formulation of amphetamine) into a pivotal study in 2017. HLD100 could further broaden treatment options for patients and physicians, if approved."

While the NDA for HLD200 has been accepted for review by the FDA, such acceptance does not mean that HLD200 will be approved by the FDA for the treatment of ADHD.

HLD200 is a novel delayed-release and extended-release formulation of methylphenidate that utilizes Ironshore's proprietary drug delivery platform, DELEXIS<sup>®</sup>, designed to enable nighttime dosing of patients with ADHD to target the onset of clinically meaningful treatment effect upon awakening and lasting through to the evening, if approved.

Ironshore Pharmaceuticals and Development, Inc., a wholly owned subsidiary of Highland Therapeutics Inc., is a pharmaceutical company that is leveraging its proprietary technology, DELEXIS<sup>®</sup>, to optimize the delivery of previously approved drug products.

Highland Therapeutics Inc. is a client of MaRS Discovery District's Health Venture Services group, which provides advisory services, connections to talent, customer, and capital networks, and market intelligence to high-impact, Ontario-based life sciences ventures, helping them commercialize their ideas and build globally competitive companies.

### Ensysce Biosciences Inc. Initiates Phase 1 Clinical Trial to Study PF614, BIO-MD™ Prodrug of Oxycodone

Business Wire: December 1, 2016 – SAN DIEGO, CA, U.S.A. – Ensysce Biosciences is pleased to announce the treatment of the first two patients with PF614, a two-step extended-release oxycodone prodrug designed to have abuse deterrent properties that limit its use to oral administration. The trial "A Phase 1, Single-Center, Dose-Escalation Study to Determine the Safety and Pharmacokinetics of a Single Oral Dose of PF614 in Healthy Subjects Compared to OxyContin<sup>®</sup>" is being conducted by Dr. Daniel Dickerson, M.D., Ph.D., of PRA Health Sciences, Lenexa, Kansas. This single ascending dose (SAD) study will treat up to six cohorts of eight healthy male and/or female subjects randomized to take PF614 or OxyContin to evaluate safety and the pharmacokinetic profile of PF614 as compared to OxyContin.

PF614 is a trypsin-activated BIO-MD<sup>™</sup> extended-release oxycodone prodrug with inherent abuse deterrence since it is pharmacologically and chemically inert until activation by pancreatic trypsin. The initial activation is followed by a second nonenzymatic cyclization and cleavage, producing free oxycodone and providing PF614 with extended release characteristics. Ensysce's product pipeline includes immediate-release (IR) or extended-release (ER) prodrugs with timed activation of opioids and stimulants that present challenges for duration of action and abuse deterrence. Additionally, Ensysce's combination MPAR<sup>™</sup> products combine the BIO-MD<sup>™</sup> prodrugs with trypsin inhibitors, providing overdose protection. The MPAR<sup>™</sup> technology has been demonstrated with PF329, an extended-release hydromorphone prodrug in a phase 1 clinical study. Ensysce prodrugs are contrasted from current and emerging opioid technologies in that they do not require elaborate formulation to confer parenteral and nasal abuse deterrence.

"Ensysce is pleased to bring PF614 into clinical development. We are focused on continuing to develop our opioid pipeline designed to significantly reduce abuse potential," said Dr. Lynn Kirkpatrick, CEO, Ensysce Biosciences. "Our prodrug approach, BIO-MD<sup>™</sup>, is well differentiated from the formulation alterations that have been marketed for these products. BIO-MD<sup>™</sup> and the combination MPAR<sup>™</sup> overdose protection products are unique in the field."

Ensysce Biosciences, San Diego, California, is an integrated drug delivery company for both small and large molecules, using prodrug technology and single walled carbon nanotubes respectively. The BIO-MD<sup>™</sup> prodrug abuse deterrent and MPAR<sup>™</sup> overdose resistant pain platforms, with worldwide intellectual patent protection, eliminate the ability to abuse opioid products by the nonoral route, the fastest growing drug problem in the United States that leads to billions in healthcare costs annually. This phase 1 clinical trial for the BIO-MD<sup>™</sup> abuse deterrent oxycodone prodrug, PF614, will provide data beginning at the end of 2016.

### November

### Ferring Pharmaceuticals and Aché Laboratórios Farmacêuticos Collaborate on Nanotechnology R&D Platform

Business Wire: November 30, 2016 – SAINT-PREX, Switzerland – Ferring Pharmaceuticals and Aché Laboratórios Farmacêuticos today announced a long-term collaboration aimed at improving the bioavailability, efficacy, and safety profile of oral therapeutic medicines through nanotechnology. Potential benefits of research in this area include a reduction of adverse effects, increased patient adherence to treatment, and more convenient dosing.

From 2017, a joint R&D centre and programme, named Nanotechnology Innovation Laboratory Enterprise (NILE), will be housed at Aché's R&D centre in São Paulo, Brazil, funded by Ferring and Aché and governed by a joint steering committee.

The centre will explore nanotechnology as a delivery system for future medicines through programmes designed to match each company's therapeutic needs. For Ferring, this means a focus on peptides and proteins in reproductive health, gastroenterology, and urology. For Aché, it represents a strategic platform to accelerate new therapeutic entity developments addressing different technical needs in order to deliver better product solutions.

"Peptides and proteins delivered orally are challenged by their inherent poor bioavailability and stability in the gastrointestinal tract, leading to less predictive therapeutic effect," said Alan Harris, senior vice president, R&D, Ferring Pharmaceuticals. "Our collaboration is focused on developing new nanotechnology-based pharmaceutical treatments to solve these challenges and better serve the needs of our patients."

"Developing new therapeutic entities by improving drug delivery characteristics of existing molecules could help improve quality of life for patients all over the world," said Paulo Nigro, CEO of Aché. "By collaborating along the R&D path in this exciting field, we will create a unique scientific environment able to tackle the main challenges in existing formulations and address unmet medical needs."

The collaboration will be inaugurated with the first NILE International Nanotechnology Workshop, taking place in São Paulo December 1–2, 2016, and featuring Brazilian and international nanotechnology experts from leading academic sites around the world.

Headquartered in Switzerland, Ferring Pharmaceuticals is a research-driven, specialty biopharmaceutical group active in global markets. The company identifies, develops, and markets innovative products in the areas of reproductive health, urology, gastroenterology, endocrinology, and orthopaedics. Ferring has its own operating subsidiaries in nearly 60 countries and markets its products in 110 countries. To learn more about Ferring or its products, please visit www.ferring.com.

Aché is a Brazilian company with 50 years of experience in the Latin American pharmaceutical market. Aché has four industrial production sites in Brazil and employs nearly 4,500 people. Half of them are focused on demand generation in the field offering a portfolio of more than 300 brands in nearly 800 submissions to meet the needs of healthcare professionals and consumers. Even though the core business is in the prescription medicines, Aché is also present in OTC, generics, skin cosmetics, and nutraceuticals. In all, 130 therapeutic classes and more than 20 medical specialties are served. Recently, with the creation of Bionovis, it has begun operating in the biotechnology field. Aché exports to 20 countries in the Americas, Africa, the Middle East, and Japan. To know more about Aché, please visit www.ache.com.br.

### Lyndra Scientists Develop Ultra Long-Acting Oral Drug Delivery Platform

Business Wire: November 16, 2016 – WATERTOWN, MA, U.S.A. – Lyndra, a healthcare company developing ultra long-acting oral drug delivery technologies, announced the publication of a scientific paper describing its novel technology in one of its earliest applications. Lyndra's revolutionary platform was initially developed at the Massachusetts Institute of Technology in the laboratory of Dr. Robert Langer. Lyndra has begun its own development work on internal and partner candidates. Lyndra's technology, which redefines ultra-long-acting oral therapeutic delivery, has the potential to transform care by improving effectiveness, reducing side effects, and creating substantial savings for patients, the healthcare system, and governments.

Data on the early use of this technology for the treatment of malaria were published today in *Science Translational Medicine*. The publication, titled "Oral Ultra Long-Acting Drug Delivery: Single Encounter Ivermectin for Malaria Elimination," describes an ingested capsule that, upon entering the stomach, assumes a geometry that prevents passage through the GI tract, enabling prolonged gastric residence. The Lyndra technology can deliver small-molecule therapies for seven days and potentially longer, and, upon the predetermined breakdown of its structure, can safely pass through the gastrointestinal tract. The study demonstrated the long-acting controlled release of ivermectin, a treatment to interrupt the vector transmission of malaria, for up to 14 days.

"This technology promises to rewrite the definition of ultra-long-acting oral therapies," said Dr. Robert Langer, Lyndra cofounder, MIT Institute Professor, and corresponding author on the paper. "Current extended and sustained release technologies achieve therapeutic serum levels for up to 12–24 hours. Lyndra's technology stands alone by pushing this timeline out to more than a week. The implications for patients are tremendous."

"People around the world depend on medications that require taking a pill every single day or even multiple times a day," said Amy Schulman, a cofounder of Lyndra and its CEO. "That approximately 50% of patients in the developed world do not take their

medicines as prescribed, a statistic that is even more challenging in the developing world, has a demonstrable effect on healthcare outcomes and a cost estimate to the U.S. healthcare system alone of over \$100 billion annually. Lyndra's long-acting technology should make a real dent in this protracted problem and help change the lives of millions of patients who feel tethered to the daily pill."

Schulman noted that Lyndra's system offers a number of clinically meaningful benefits including convenient, once weekly (or less frequent) oral dosing, improvements in patient adherence, near constant therapeutic serum levels with more predictable pharmacodynamics, and potential of side effect reductions due to decreased variability of drug concentration. Safety mechanisms to prevent obstruction of food, perforation, mucosal injury, and other adverse events are built into the design of Lyndra's polymer-based system.

Lyndra's next applications extend beyond infectious disease, including chronic diseases such as psychiatric disease, renal disease, and addiction. Lyndra will initiate clinical trials for its primary internal product in mid-2017. Lyndra is also partnering with a select number of leading pharmaceutical and biopharmaceutical companies to develop ultra-long-acting oral products of their proprietary small molecule therapies. Each product will undergo preclinical and clinical testing to satisfy regulatory requirements before being made available to the public.

The study was published today in *Science Translational Magazine*. Authors include Andrew Bellinger, MIT, Harvard Medical School, Lyndra; Mousa Jafari, MIT; Tyler Grant, MIT, Lyndra; Shiyi Zhang, MIT; Hannah Slater, Imperial College London; Edward Wenger, Institute for Disease Modeling; Stacy Mo, MIT; Young-Ah Lucy Lee, MIT; Hormoz Mazdiyasni, MIT; Lawrence Kogan, MIT; Ross Barman, MIT; Cody Cleveland, MIT and Harvard Medical School; Lucas Booth, MIT; Taylor Bensel, MIT; Daniel Minahan, MIT; Haley Hurowitz, MIT; Tammy Tai, MIT; Johanna Daily, Einstein Medical College; Boris Nikolic, Biomatics Capital; Lowell Wood and Philip Eckhoff, Institute for Disease Modeling; Robert Langer, MIT; and Giovanni Traverso, MIT and Harvard Medical School.

Lyndra aims to fundamentally change the way patients take medicines through the development of oral, ultra-long-acting, sustained release oral therapies that drastically improve healthcare outcomes. The Lyndra technology was developed at the Massachusetts Institute of Technology, in the laboratory of Dr. Robert Langer in collaboration with the Bill and Melinda Gates Foundation. Lyndra formulations transform medications taken daily or more frequently into a weekly or monthly dose, promising to improve patient adherence as well as to optimize the pharmacokinetic profile of the dosage form.