

What's Inside

Modern Drug–Medical Device
Combination Products

Controlled Release of Levofloxacin
from Vitamin E Loaded Silicone-
Hydrogel Contact Lenses

Encapsulation of Gold
Nanoparticles to Visualize
Intracellular Localization of Lipid
and Polymer-Based Nanocarriers

The One Health Initiative and Its
Impact on Drug Development

DDTR Update

Chapter News



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CRS Newsletter

Leading
Delivery Science
and Technology

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> TABLE OF CONTENTS

- 4** **From the Editor**
- 5** **Preclinical Sciences & Animal Health**
The One Health Initiative and Its Impact on Drug Development
- 8** **Special Feature**
Modern Drug-Medical Device Combination Products
- 10** **Scientifically Speaking**
Controlled Release of Levofloxacin from Vitamin E Loaded Silicone-Hydrogel Contact Lenses
- 12** **Scientifically Speaking**
Encapsulation of Gold Nanoparticles to Visualize Intracellular Localization of Lipid and Polymer-Based Nanocarriers
- 15** **CRS Foundation**
2016 Allan Hoffman Student Travel Grant Program
- 16** **Chapter News**
Drug Delivery Australia
- 18** **Chapter News**
Rheology: How to Get into the Flow
- 20** **Chapter News**
Micro- and Nanotechnologies to Overcome Biological Barriers: Eighth Annual CRS Italy Local Chapter Workshop
- 22** **DDTR Update**
Drug Delivery and Translational Research Update
- 24** **People in the News**
- 25** **Companies in the News**

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Roderick B. Walker
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Wanted: Innovative, Translatable Science

January and February have flown by, and 2016 is well on its way. However, it would be remiss of me not to wish you all, on behalf of CRS and the newsletter team, a happy, prosperous, productive, and successful year.

This first *CRS Newsletter* issue for 2016 takes us to Italy, New Zealand, and Australia with updates from local chapters on their local conferences and workshops. By all accounts these were very successful meetings that provided updated information in current trends in drug delivery. There is an article dealing with the One Health initiative that makes for fascinating reading, and I look forward to next piece in this three-part series. The feature article titled "Modern Drug-Medical Device Combination Products" provides insight into the many opportunities that we as delivery scientists can harness creatively as we attempt to solve difficult health challenges that face the global population. Some of this innovation we see in the Scientifically Speaking articles in this issue, and I am sure there will be much more to come in the future. Of particular importance is the need to translate our inventions into usable technologies, and there are some papers in the *DDTR* journal that reveal what is possible if we harness the power of the science when seeking to ensure that the right to health is achieved by all persons on the planet.

The *CRS Newsletter* itself has changed from a print to a digital format, with design features that will make it easy to read. In addition, since we know you all look forward to the contents of the newsletter, you will no longer have to wait two months between issues to read the excellent contributions made by scientists from all over the world. Articles will be available early online, and visiting the home page regularly will allow you to be up to date with what is on offer in the newsletter. In the future, there may also be video to enhance the experience.

There are many challenges facing the world; however, by asking the right questions about some of the challenges there will be opportunities to use our expertise in delivery science to be innovative and develop translatable solutions to improve the health and well-being of all inhabitants in the world. May 2016 be your year to make a difference. ■



The One Health Initiative and Its Impact on Drug Development

Marilyn Martinez^a and Terry Bowersock^b

The One Health concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals, and the environment. The goal of this initiative is to improve the lives of all species through knowledge integration (www.onehealthinitiative.com/about.php). The strength of the One Health concept is evidenced by the upsurge in articles involving translational research and the growth of translational research groups within veterinary and medical schools. There also are information databases that describe the genes associated with various diseases across human and preclinical (animal) species (e.g., www.Qiagen.com).

The lifespan of companion animals has been increased, leading to the need for long-term treatment of chronic diseases and the onset of age-associated degenerative conditions that parallel those observed in people. Similarly, there are a wide range of shared naturally occurring diseases in dogs and people including arthritis, spinal cord injuries, hemophilia, cleft palate, lysosomal storage disease, inflammatory bowel disease, and several cardiomyopathies. Interestingly, because of a naturally occurring frameshift mutation in the NKX2-8 gene that was shown to cause neural tube defects in Weimaraners, researchers examined and identified rare NKX2-8 missense mutations that were significantly overrepresented in a cohort of 149 human patients with spina bifida, suggesting its role in the pathogenesis of this disease.¹

These similarities have resulted in a new term, “zoobiquity,” that reflects efforts to explore how human and nonhuman animal commonalities can be used to diagnose, treat, and heal patients of all species (www.zoobiquity.com). Recognizing that animals and humans share many of the same diseases, the challenge is identifying constraints associated with the translation of scientific and medical/therapeutic information across species lines. This includes exploring commonality of disease (etiology and expression), comparison of genetic and epigenetic regulators, and the development of therapies and delivery systems that can be safely and efficiently employed to achieve effectiveness across species lines. This effort has led to a movement to enhance communication between experts in laboratory science and clinical medicine for the purpose of developing novel therapeutics to prevent, diagnose, and treat disease.

In the past, the focus has been on the use of animal models that are based upon induced diseases. Such preclinical studies often prove to be poor predictors of therapeutic outcomes in human clinical trials.¹ A problem associated with these models is that the disease progression and etiology may be markedly different from that of naturally occurring disease. Examples of reasons for this failure include the following:²⁻⁵

- Animal stress: this can include “contagious anxiety,” in which a fight or flight reaction is induced by animal awareness of procedures conducted on their cohorts. In fact, stress can cause inflammatory conditions that can alter intestinal permeability (i.e., increase leakiness) and neurochemistry.
- Organ structure, which leads to differences in the disease targets.
 - For example, human pancreatic islet cells are critical to the development of human diabetes, which is very different from that of rodents, leading to difficulty in extrapolating data generated in the rodent diabetic animal model.
 - Another example is the model for human stroke, which often relies on the clamping of blood vessels in the animal model. This method of stroke induction does not resemble the clot or plaque-induced perfusion failure that occurs in humans. Therefore, it is not surprising that >150 stroke drugs found to be effective for stroke in animal models failed to reproduce similar positive therapeutic effects in humans.
- Gene expression of genetically altered animals may have different expression characteristics compared with that of humans. This can lead to potentially misleading experimental results.

continued

^a U.S. Food and Drug Administration, U.S.A.

^b Zoetis, LLC (formerly Pfizer Animal Health), U.S.A.

Thus, we are often left with data that are more closely aligned with that of the animal model of the disease than of the actual human disease.

A hub of this type of synergistic collaboration is the University of Pennsylvania Veterinary Clinical Investigations Center. On their website (<http://research.vet.upenn.edu/TranslationalResearch/tabid/4413/Default.aspx>), they provide the following list of advantages associated with the study of human diseases in companion animals:

- The conditions can be naturally similar biologically, histologically, and in clinical course.
- Since the disease is not induced, complex and sometimes unexpected tissue interactions can be studied.
- Many diseases are the consequence of complex interactions with environmental factors; therefore, it is relevant that pets share a common environment with people.
- Heterogeneity and diversity of the pet population are more similar to people than rodent models.
- Comparative genomic analysis suggests significant similarity between canine and human lineage in such things as nucleotide divergence and rearrangements.
- Sampling is easier in companion animals compared with rodents.
- Diagnostic and monitoring technologies comparable to human patients are used in veterinary patients.
- The physiology of the dog is such that it responds to and metabolizes drugs in a comparable way to humans, which is why dogs and cats are routinely used for pharmaceutical and toxicological studies.
- Treating naturally occurring disease does not attract the ethical dilemmas seen with experimentally induced disease.
- Data collected is useful both as clinical data for veterinary patients and preclinical data for human patients.

The translational research team at the University of Pennsylvania are bridging the gap between bench and bedside by conducting clinical trials with client-owned dogs and cats. Conventionally, new medical advancements move from experiments with laboratory animals, such as mice, rats, and pigs, directly to human clinical trials. However, through the use of client-owned dogs and cats, scientists, veterinarians, and physicians acquire an appreciation of the outcome of therapeutics in patients whose day-to-day lives more closely resemble our own. While laboratory animals live in a very controlled setting, our pets live in our homes, sometimes eat what we eat, and experience the environment in a similar way that we do. Not only does translational medicine in the veterinary setting benefit the pets we aim to treat, but it also brings us one step closer to treating humans with comparable disease processes.

Another hub of translational activity is the University of Missouri–Columbia, where they are bridging potential therapeutics for shared diseases such as naturally occurring Duchene muscular dystrophy (DMD) in dogs and people.⁶ DMD is a genetic defect that leads to the replacement of damaged muscle tissue with fibrous, fatty, or boney tissues, leading to the loss of muscular function. It appears to be associated with to a gene mutation that disrupts the production of dystrophin. The absence of dystrophin starts a chain reaction that eventually leads to muscle cell degeneration and death. A homologous disease to DMD exists in dogs. Owing to its size, it is impossible to deliver the entire gene with a gene therapy vector. However, scientists were able to develop a miniature version of this gene (a microgene) that protected all muscles in the body of diseased dogs and humans. The dogs were injected with the virus when they were two to three months old and just starting to show signs of DMD. As reported, at six to seven months old the dogs continued to develop normally. This microgene will soon be used in humans.

Translational research reaches beyond animals that express diseases and segues into exploring why some animal species do not get certain diseases. For example, Peto's paradox is a term applied to efforts to understand why certain species such as whales or elephants, which have 1,000-fold and 100-fold more cells than humans and a long lifespan, do not exhibit a higher cancer risk than humans. The observation that the amplification of certain suppressor genes, such as TP53, occur in these "cancer immune" species may help to explain the absence of the correlation between size, lifespan, and cancer risk.⁷ It appears that in elephants, TP53 may be related to an increased apoptotic response following DNA damage.⁸

In addition to therapies, companion animals provide an opportunity to develop and refine diagnostic tests. State-of-the-art diagnostic tools such as immunohistochemistry, molecular diagnostics, and advanced imaging modalities are part of the diagnostic arsenal in veterinary medicine. Similarly, delivery of advanced therapeutic regimens may include organ transplantation, transfusion medicine, minimally invasive and reconstructive surgery, and advanced chemotherapy and radiation protocols.¹

Companion animals also develop spontaneous neoplasms that are effectively 100% homologous to those seen in people. In combination with the dog's shorter lifespan and rapid disease progression, this natural model of disease provides a tremendous opportunity to develop parallel treatments in people and dogs. This is in contrast to the rodent cancer models, whose successful translation of therapeutics to human clinical trials is less than 80%. It also appears that canine and human cancers are influenced by age and environment. Furthermore, dog tumors are histologically similar to human cancers, frequently showing the same tumor oncogenes and suppressor genes.⁹

From a formulation development perspective, interspecies extrapolation of drug product pharmacokinetics and drug product performance should typically proceed with caution owing to known physiological differences that can influence *in vivo* product performance.¹⁰ Such extrapolations can be particularly challenging when bridging between rodent models and humans. Altered drug partitioning into the site of action can occur in the presence of disease, but the use of naturally occurring diseases rather than rodent models can improve predictions of drug delivery to the site of action. Accordingly, the One Health initiative may reduce many of the uncertainties associated with interspecies extrapolations.

In our second article in this series, we will provide further discussion of the commonality of cancer and cancer treatments in dogs and people.

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Modern Drug–Medical Device Combination Products

Ronald A. Siegel¹ and SuPing Lyu²

Drugs and medical devices represent two modalities in treating disease, which display some fundamental differences. Drug molecules, when administered by conventional means, rarely remain in the body at therapeutic levels for extended time periods. Implantable devices such as pacemakers and vascular grafts, on the other hand, are usually designed to persist within the body and maintain their function for extended periods of time. (Exceptions to the rule occur for implanted devices that are meant for short-term purposes. Such devices can be retrieved later or can be programmed for degradation and resorption.)

Devices have long been used to improve drug therapy. Tablets, capsules, oral liquid syringes, eye drops, nose drops, syringes for intravenous, subcutaneous, or intramuscular injection, and catheters are classical drug delivery devices. While these devices continue to be perfected, the last 50 years has seen the introduction of numerous advanced drug delivery devices that are designed to improve the timing and placement of drug administration. The motivation behind such spatiotemporal control has been due, in part, to improved understanding of the roles of pharmacokinetics (ADME), mass transport through biological barriers, receptor-mediated pharmacodynamics, and toxicology in determining how a drug should best be administered. Members of CRS need only think of external or implantable electromechanical pumps, osmotic pumps, passive- and electrotransport-driven skin patches and microneedle arrays, ocular inserts, and specially designed intranasal and pulmonary applicators (which control the location in the nasal cavity or lung in which particles are deposited) as examples in which mechanical, chemical, and electrical devices can improve drug delivery. Other devices include injectable micro- and nanoparticles, whose physical (size, porosity) and chemical (targeting ligands, degradation) properties are designed in to optimize the spatial and temporal distribution of the active agent.

The previous paragraph emphasizes the use of devices to improve drug therapy. Conversely, how can drugs enhance device therapy? Insertion of any device involves some insult to the local tissues and may result in infection due to incomplete sterility of the procedure, local inflammation, the inevitable foreign body reaction, or a systemic immune response. Traditionally, this challenge has been met by administering antibiotics, anti-inflammatories, and immune response modifiers before, during, or after the procedure. Well-known examples include oral penicillin used as an adjunct to oral surgery (often involving installation of a periodontal device) in order to prevent bacterial colonization on susceptible heart valves, and prescription of Plavix to prevent inflammation following surgical placement of a coronary stent. Along similar lines, transcutaneous catheters are notoriously susceptible to infection, and much interest has been shown in coating the lumens of such catheters with antibiotics that elute throughout the period of catheterization.

Systemic administration of drugs following a surgical or local incision procedure can treat acute reactions without significant danger to the patient. However, chronically implanted devices may require more sustained delivery to ameliorate local reactions, and long-term systemic delivery of pharmacologic countermeasures is out of the question due to issues of convenience, compliance, and eventual onset of toxicity as drug accumulates throughout the body. For this reason, considerable effort has been expended in developing drug/device combination products, especially for chronic conditions. In the next few paragraphs, we provide examples.

Cardiac rhythm control, or pacemaking, has been one of the most significant developments in modern medicine and has saved millions of lives. While early pacemakers were bulky and required transcutaneous delivery of current from an external power source to the implanted pacemaker lead, advances in microprocessing and battery technology have permitted total implantation. The pacemaker lead is placed directly into the myocardium, where it delivers pacing current pulses. After placement of the lead, however, a fibrous capsule forms around it, increasing the resistance of the lead-myocardial interface. By Ohm's law, voltage = current \times resistance, the voltage required to maintain the required current

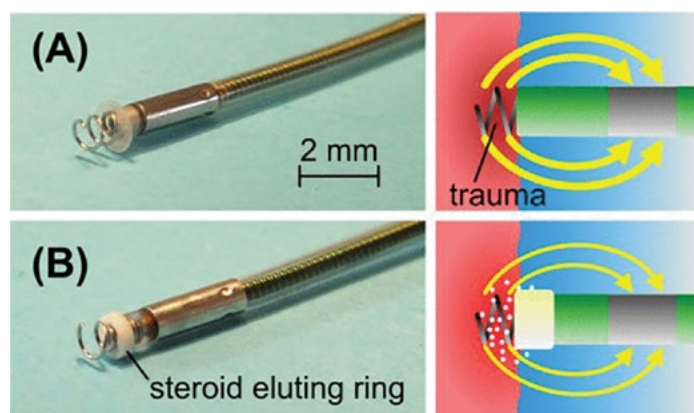


Figure 1. Cardiac pacemaker lead (type KY-5, Osypka, Rheinfelden-Herten, Germany) without (A) and with (B) a steroid-eluting ring. Yellow arrows in the panels to the right denote electrical current path. In the absence of the ring, trauma leads to buildup of capsular tissue, which impedes current flow and requires larger power drainage, shortening battery life. (©IEEE. Reprinted, with permission, from S. Herrlich et al., Drug release mechanisms of steroid eluting rings in cardiac pacemaker lead electrodes, *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012:681–684. [ncbi.nlm.nih.gov/pubmed/23365984](https://pubmed.ncbi.nlm.nih.gov/23365984/))

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must increase. According to the power relation, power = voltage \times current, the amount of power per pulse also increases, and power is drained from the battery more rapidly, shortening the battery's lifetime. Recognizing this problem, pacemaker leads are regularly accompanied by small cuffs, which slowly and steadily release anti-inflammatory steroids such as dexamethasone into the surrounding myocardial tissue (Figure 1). The steroid attenuates formation of the fibrous capsule, keeps electrical resistance and power drainage low, and enhances battery lifetime. Because the steroid is targeted directly to the cardiac tissue, its dosing rate is a tiny fraction of what would be required if the steroid were administered systemically, and toxic side effects are negligible.

A second class of devices that have benefited from local drug release are coronary stents. Following a heart attack, the enzyme streptokinase is injected into the thrombotic coronary artery, dissolving the clot and permitting reestablishment of blood flow. Then, a stent consisting of a metal mesh, surrounding an inflatable balloon, is threaded into the coronary artery at the tip of a guiding catheter under angiographic visualization. Once properly situated, the balloon is inflated and the stent ratchets into place, keeping the artery open. The catheter and balloon are then withdrawn. The earliest coronary stents were made of bare, polished stainless steel. While these "bare metal" stents were successful in maintaining structural integrity of the arterial walls, regrowth of arterial smooth muscle and epithelium into the arterial lumen, or restenosis, occurred in about 25% of the surgical patients. To alleviate this problem, various anti-inflammatory (e.g., sirolimus) and anti-proliferative (e.g., paclitaxel) drugs are sprayed onto the stent surfaces in conjunction with a

polymer, which controls the rate of release of the drug into the surrounding arterial tissues over a prescribed time period, thus attenuating inflammatory and/or neoproliferative processes. Such drug-eluting stents (Figure 2) are masterpieces of engineering, because they must be designed to release drug in a controlled manner over weeks to months, such that a large fraction of the released drug is available to the local tissue, and such that the coating film does not detach from the underlying metal. As with the steroid-eluting lead, it is possible to achieve high local concentrations of the drug while avoiding significant buildup of drug levels elsewhere in the body. Drug-eluting stents have been shown to reduce the restenosis rate to about 5%.

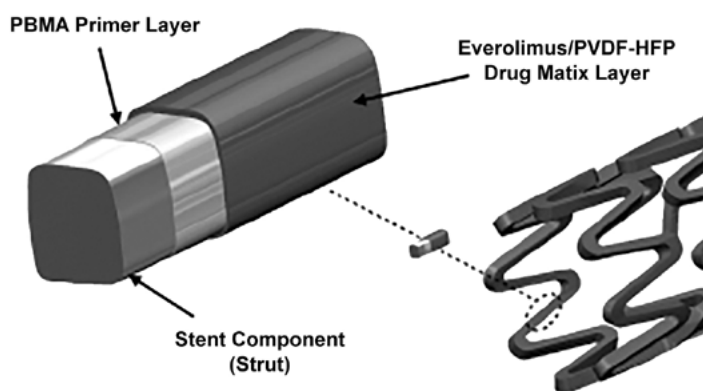


Figure 2. Structure of a drug-eluting stent (Promus Element, Boston Scientific). At right is a diagram of a fully expanded stent. At left is a blowup showing the metal stent component, or strut, which is covered first by a primer layer of poly(butyl methacrylate) (PBMA) and then a layer of the anti-inflammatory drug everolimus dispersed in a semi-crystalline random copolymer of vinylidene fluoride and hexafluoropropylene (PVDF-HFP). (©Wiley. Reprinted, with permission, from Y.-L. Chen and K. Robertson, *Promus Element™ Plus®: A drug-eluting stent*, in *Drug-Device Combinations for Chronic Diseases*, ed. S. Lyu and R. A. Siegel, Wiley–Society for Biomaterials, 2016.)

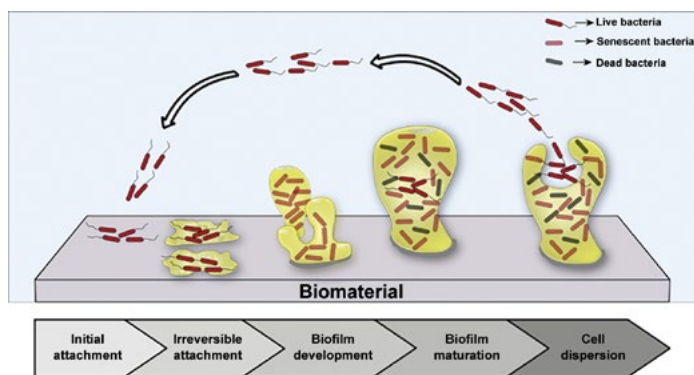


Figure 3. Bacterial seeding, colonization, biofilm transformation, differentiation, maturation, and further dissemination produced following biomaterial-associated contamination and infection. (©Wiley. Reprinted, with permission, from M. H. Avula and D. W. Grainger, *Addressing medical device challenges with drug-device combinations*, in *Drug-Device Combinations for Chronic Diseases*, ed. S. Lyu and R. A. Siegel, Wiley–Society for Biomaterials, 2016.)

While we have focused primarily on cardiac applications, local drug delivery may serve to increase the patency and efficacy of other devices used to treat a variety of target conditions. Another important application is to maintain a microbe-free environment surrounding an implanted device. Any incision poses risk of microbial infection, and bacteria are notoriously effective in forming colonies, or biofilms, on surfaces. Following colonization, bacteria go into a dormant state, but some unpredicted triggering event, which may happen years later, "wakens" the bacteria, which then detach and invade the blood stream. Bacteria in biofilms are highly resistant to antibiotic therapy and require much higher doses compared with circulating, planktonic bacteria (Figure 3). Incorporation of antibiotics near or on the surfaces of medical devices may prevent them from being colonized.

While it may seem simple to combine already utilized drugs and devices, experience in the industry has shown that it may take years of development to get it right. Regulatory agencies are also concerned with the compounding of risks whenever a combination therapy is proposed. We see combination drug/device therapies as having great future promise, but much needs to be learned regarding how they can be developed optimally.

Ronald A. Siegel and SuPing Lyu are co-editors of a recent book titled *Drug-Device Combinations for Chronic Diseases* (Wiley–Society for Biomaterials, 2016). For more information, visit wiley.com/WileyCDA/WileyTitle/productCd-1118120000.html. ■

Controlled Release of Levofloxacin from Vitamin E Loaded Silicone-Hydrogel Contact Lenses

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Introduction

Nowadays, most of the currently available ocular drugs are administered topically through eye drops,¹ but their residence time in the eye is short, about 2 min. Only 1–7% of the dose delivered from an eye drop is absorbed by the eye, leading to a final poor drug bioavailability and in some instances to side effects.²

In the last few years, efforts have been made in the attempt to develop new and more efficient ophthalmic drug delivery systems. Among other vehicles, therapeutic soft contact lenses have been demonstrated to be an ideal platform for the controlled delivery of numerous drugs as well as molecules that provide eye comfort.³

To increase drug release duration, Chauhan and coworkers have explored the effect of incorporating vitamin E in contact lenses to create diffusion barriers that can lead to extended release of several ophthalmic drugs.^{4,5} The hydrophobic and poorly aqueous soluble vitamin E precipitates at the interphase of the biphasic silicone material and acts as a physical chemical barrier to drug diffusion inside the hydrogel.

Bacterial keratitis is a common affliction of the eye, and it is commonly treated by frequent instillation of eye drops. The broad spectrum antibiotic levofloxacin (LVF) (e.g., QUIXIN®, concentration 5 mg/mL) is currently one of the most used drugs for the therapy and prophylaxis of eye infections caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

In the present work, the release of LVF from the commercial silicone-based contact lens ACUVUE® TrueEye, preloaded with vitamin E, was investigated. To confirm their adequacy to the ophthalmologic use, the lenses were characterized with respect to their transmittance, wettability, and ionic permeability.

Experimental Methods

Vitamin E and drug loading steps are detailed in Figure 1. ACUVUE® TrueEye lenses were soaked in vitamin E solution dissolved in ethanol (42 mg/mL) for 3 h. Lenses were withdrawn from the solutions, gently blotted, and dried overnight in air, obtaining a vitamin E final w/w fraction of 20%. For the drug loading step, LVF (28266, Sigma Aldrich) was dissolved in phosphate-buffered saline (PBS) (5 mg/mL). Vitamin E loaded lenses were soaked in this solution for 7 days. For the control, the vitamin E loading step was skipped.

Drug release experiments from control and vitamin E loaded contact lenses were performed in sink conditions in 3 mL of PBS, at room temperature. At predetermined time intervals, the absorbance spectra of the supernatant solution were measured over the wavelength range of 265–305 nm using a UV-visible spectrophotometer (Thermospectronic Genesys 10 UV).

The ion permeability of the lenses was assessed by measuring the release profiles of salt in sink conditions ($n = 3$). Lenses were previously soaked in 0.75M NaCl solution overnight to load the salt. The release was done into 36 mL of well-stirred (300 rpm) deionized water. The NaCl concentration of the aqueous medium was monitored using a Con 110 series sensor (OAKTON®).

Optical clarity studies were carried out measuring the transmittance of the lenses with a UV-visible Beckman DU-70 spectrophotometer. Three independent experiments were done.

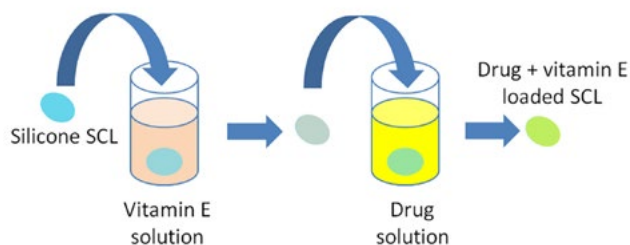


Figure 1. A schematic representation of the methodology of vitamin E and drug loading into the ACUVUE® TrueEye™ lens. SCL = soft contact lens.

continued

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The wettability of the hydrated contact lenses was characterized by measuring the water contact angles through the captive bubble method. Bubble images were acquired using a video camera (JAI CV-A50) attached to a microscope (Wild M3Z), which was connected to a frame grabber (Data Translation DT3155). The image analysis was performed with ADSA-P software (axisymmetric drop shape analysis profile).

Results and Discussion

Figure 2 shows LVF release profiles in fresh PBS from ACUVUE® TrueEye™ lenses with and without vitamin E. The lenses released 90% of the loaded drug in 32 h. With the inclusion of 20% vitamin E, the drug release duration (for 90% of the total mass released) increased to 100 h, exhibiting a threefold increase of the release time. The mass of drug released was not impacted by vitamin E incorporation. The lenses were subjected to a second cycle of release to test the validity of the sink assumption. The data showed negligible release of LVF in the second release cycle, proving that the release conditions for the first cycle can be considered as sink, and that the total amount of drug loaded was released.

The ion permeability of the control lenses was $1.1 \times 10^{-7} \pm 0.6 \times 10^{-7} \text{ cm}^2/\text{s}$ ($n = 3$), and it decreased to $0.7 \times 10^{-7} \pm 0.4 \times 10^{-7} \text{ cm}^2/\text{s}$ ($n = 3$) in the presence of vitamin E. In both cases the ion permeability was above the minimum acceptable value ($2.5 \times 10^{-8} \text{ cm}^2/\text{s}$).⁶

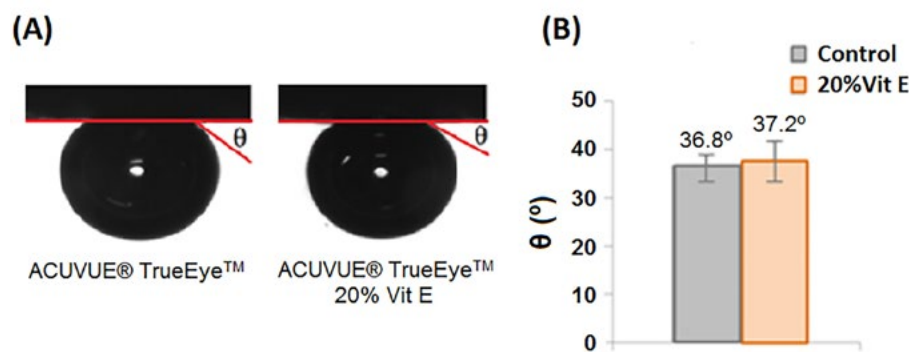


Figure 3. Wettability measurement results through the captive bubble technique. (A) Representative bubble profiles. (B) Water contact angle values measured with and without vitamin E incorporated into the contact lenses. Error bars represent the standard deviations ($n = 8$).

ionic permeability. The increase in duration happens owing to the presence of the vitamin E nanoaggregates formed into the lenses, which have a barrier effect for the drug release. The drug release duration achieved shows that a contact lens would cover the most acute phase of bacterial keratitis, avoiding the annoying instillation of eye drops during the first 4 days. For a detailed treatment of this topic, see our upcoming article “Controlled Release of Antibiotics from Vitamin E–Loaded Silicone-Hydrogel Contact Lenses” in *Journal of Pharmaceutical Sciences*.

Acknowledgements

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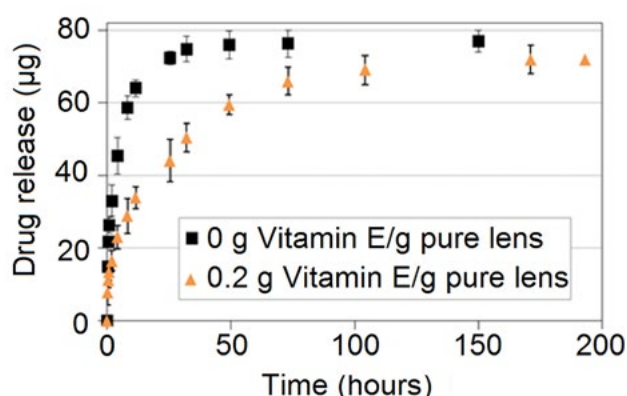


Figure 2. Cumulative drug mass released from the ACUVUE® TrueEye™ (black square) control lens and the vitamin E loaded (orange triangle) lens. Error bars represent the standard deviations ($n = 3$).

The presence of vitamin E caused a decrease in the transmittance by about 5%, but both samples (with and without vitamin E) presented values of transparency over 90%, matching the transmittance characteristics of soft contact lenses.

The contact angle results (Figure 3) showed that the presence of vitamin E did not significantly alter the wettability.

Conclusion

Vitamin E loading in commercial silicone contact lenses can evidently increase the release duration of LVF antibiotic, without compromising transparency, wettability, and

Encapsulation of Gold Nanoparticles to Visualize Intracellular Localization of Lipid and Polymer-Based Nanocarriers

Dominik Witzigmann,^a Sandro Sieber, Fabiola Porta, Philip Grossen, Andrej Bieri, Natalja Strelnikova, Thomas Pfohl, Cristina Prescianotto-Baschong, and Jörg Huwyler
University of Basel, Switzerland

Introduction

Nanoparticulate drug delivery systems offer a huge potential for various biomedical applications, and the number of related research projects has been increasing constantly over the last decade.¹ The delivery of small molecules, proteins, or nucleic acids to target cells using nanocarriers has several advantages compared with conventional therapeutics. Therefore, the examination of cellular uptake and intracellular trafficking of nanocarriers has become an important research field with great implications for the therapeutic outcome of nanomedicines.^{2,3} Encapsulation of electron dense nanoparticles into nanocarriers is an interesting option for bioimaging using electron microscopy and therefore examination of subcellular localization. Gold nanoparticles (AuNPs) especially have attracted great attention owing to their unique properties including (1) advantageous physicochemical characteristics, (2) nontoxic and inert properties, (3) facile preparation of monodisperse AuNPs, and (4) various modification options.⁴ In recent decades, great progress has been made in the field of hybrid nanocarriers using AuNPs. However, the formation approaches exhibited marked variability in homogeneity, reproducibility, size distribution, and morphology of hybrid nanocarriers (i.e., nanocarriers encapsulating AuNPs [AuNHyb]). To overcome these challenges, we developed a novel and versatile strategy to encapsulate AuNPs into different nanocarriers with high reproducibility using a “nanoreactor approach.” In this study, we encapsulated a reaction solution (tetrachloroaurate/citrate mixture) within the interior of nanocarriers and initiated the AuNP formation after self-assembly of the nanomaterial. Different nanomaterials such as lipids or polymers were validated, and the encapsulation efficiency, homogeneity, and robustness of our approach were optimized. Intracellular trafficking of these hybrid nanocarriers *in vitro* was performed using transmission electron microscopy (TEM).

Experimental Methods

Various nanocarriers such as conventional liposomes (POPC/POPG; Figure 1), di-block copolymer nanoparticles (PEG-PCL; Figure 2), or PEGylated stealth liposomes (PEG-DSPE/DSPC/cholesterol; Figure 3) were produced using the filmrehydration-extrusion, nanoprecipitation, or microfluidics method, respectively. After the self-assembly process the different nanocarriers encapsulated a reaction solution consisting of tetrachloroaurate and citrate. A temperature shift to 70°C initiated the formation of AuNPs inside the nanocarriers. To remove nonencapsulated AuNPs, size-exclusion chromatography was performed. The physicochemical characteristics of our lipid and polymer AuNHybs were evaluated using dynamic light scattering (DLS), TEM, CryoTEM, and UV-visible spectroscopy. To examine the application of AuNHybs as a bioimaging tool, we performed cellular uptake experiments in HepG2 cells and used the electron density of AuNPs for further TEM analysis (Figure 4). For detailed experimental procedures, see Witzigmann et al.⁵

Results and Discussion

For the preparation of AuNP-loaded nanocarriers, the most direct approach is the use of presynthesized AuNPs. However, the encapsulation of preformed AuNPs has several issues, including low encapsulation efficiency (data not shown). Therefore, we developed an alternative strategy and combined a variety of preparation methods with our nanoreactor approach (Figures 1–3, panel A). The formation of AuNPs inside the nanocarriers was initiated after self-assembly by a temperature shift. The most important factor of our approach was the fast production of nanocarriers at room temperature (RT) to avoid the formation of AuNPs before self-assembly.

continued

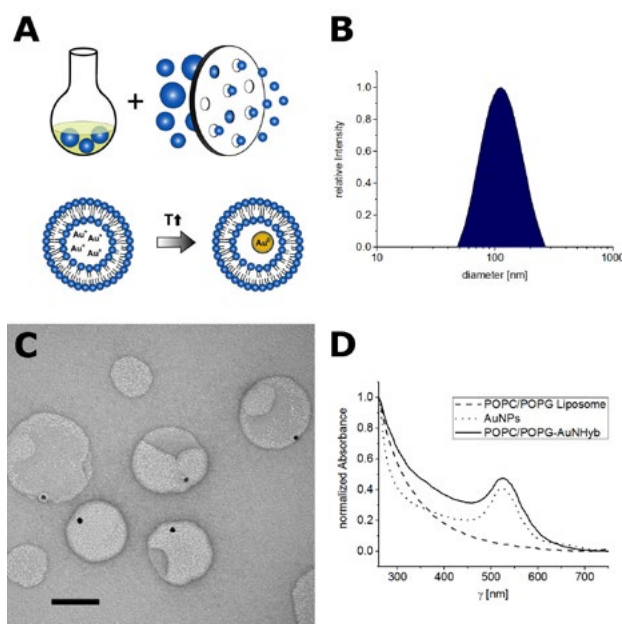


Figure 1. Conventional liposomes (POPC/POPG) loaded with gold nanoparticles (AuNPs). (A) Schematic representation of the filmrehydration-extrusion method for lipids with $T_m < \text{room temperature}$. (B) Dynamic light scattering analysis of size distribution. (C) Representative TEM images. Scale bar = 100 nm. (D) Relative UV-visible absorption. AuNPs and gold loaded nanocarriers (AuNHybs) show a characteristic surface plasmon band at approximately 525 nm.

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Adapted from Witzigmann et al. (<http://dx.doi.org/10.1039/C5RA13967H>)⁵ with permission from The Royal Society of Chemistry.

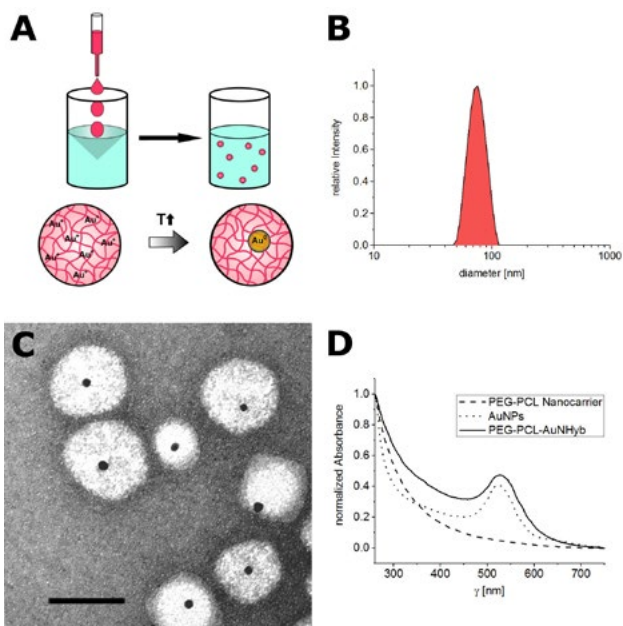


Figure 2. Di-block copolymer nanocarriers (PEG-PCL) loaded with gold nanoparticles (AuNPs). (A) Schematic representation of the nanoprecipitation method. (B) Dynamic light scattering analysis of size distribution. (C) Representative TEM images. Scale bar = 100 nm. (D) Relative UV-visible absorption. AuNPs and gold loaded nanocarriers (AuNHys) show a characteristic surface plasmon band at approximately 525 nm.

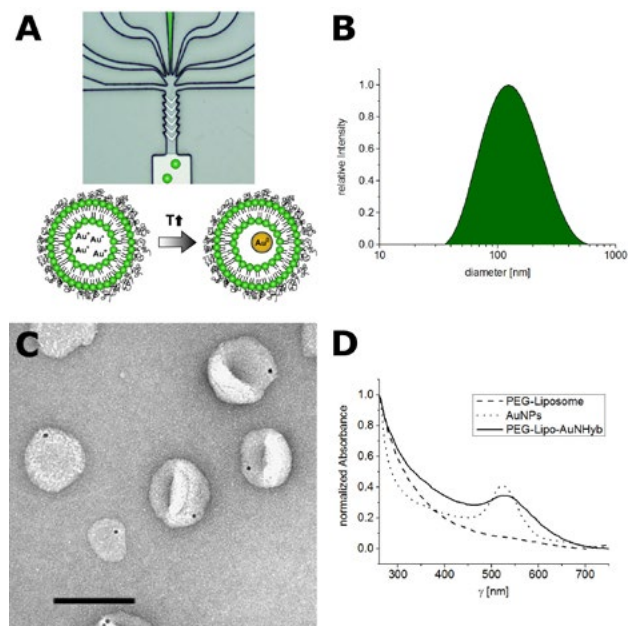


Figure 3. PEGylated stealth liposomes (PEG-DSPE/DSPC/cholesterol) loaded with gold nanoparticles (AuNPs). (A) Schematic representation of the microfluidics platform for lipids with $T_m >$ room temperature. (B) Dynamic light scattering analysis of size distribution. (C) Representative TEM images. Scale bar = 100 nm. (D) Relative UV-visible absorption. AuNPs and gold loaded nanocarriers (AuNHys) show a characteristic surface plasmon band at approximately 525 nm.

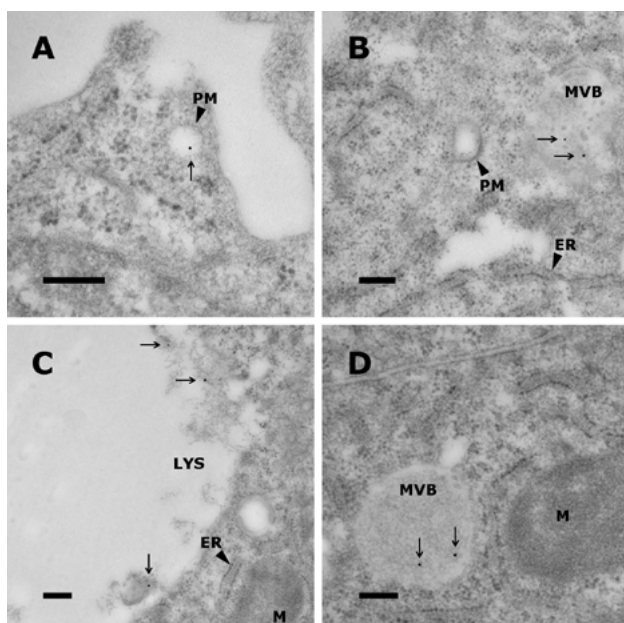


Figure 4. Uptake experiments of gold loaded nanocarriers (AuNHys) in HepG2 cells. Representative uptake images of (A and B) POPC/POPG AuNHys and (C and D) PEG-PCL AuNHys. Different internalization steps and subcellular localizations can be observed. ER = endoplasmatic reticulum; LYS = lysosome; M = mitochondria; MVB = multi-vesicular body; and PM = plasma membrane. Scale bars indicate 200 nm.

The film rehydration method is suitable for lipids with a transition temperature below RT (Figure 1), whereas the nanoprecipitation method is suitable for various polymer nanomaterials (Figure 2). The microfluidics method is especially designed for lipids with a transition temperature above RT, because the film rehydration method above RT is not compatible with the nanoreactor approach (Figure 3). In general, microfluidics is suitable for all nanomaterials that need highly controlled nanomanufacturing. In addition, this technique offers the possibility for efficient and large-scale production.

In contrast to other methods for AuNP encapsulation, we achieved a high homogeneity and produced nanocarriers with a monodisperse size distribution (polydispersity index < 0.2) (Figures 1–3, panel B). The hydrodynamic diameter of AuNHys determined by DLS was between 50 nm and 120 nm, which is in the size range of nanocarriers for biomedical applications. The AuNPs were encapsulated within the AuNHys, as clearly visualized by electron microscopy (Figures 1–3, panel C). All AuNHys exhibited a characteristic ruby-red color resulting from the surface plasmon resonance of incorporated AuNPs (Figures 1–3, panel D).

Passive uptake experiments of AuNHys into HepG2 cells demonstrated the applicability as a bioimaging tool (Figure 4). AuNHys could be used to examine nanoparticle-cell interactions and the intracellular fate of nanocarriers by TEM, allowing a considerably higher resolution compared with confocal laser scanning microscopy. However, if needed, AuNHys could be combined with fluorescent dyes to offer additional possibilities such as live cell imaging (data not shown).

continued

Conclusion

In conclusion, we have developed a novel AuNP encapsulation technique for lipid and polymer-based nanocarriers. Via this nanoreactor approach, a high AuNP encapsulation efficiency was achieved. To the best of our knowledge, this study is unique in applying different nanomaterials in combination with various preparation methods. The high reproducibility and versatility of our nanoreactor approach is unprecedented and makes this technology suitable for many nanomaterials. In the future, our nanoreactor approach will be instrumental to develop a better understanding of cellular uptake and intracellular trafficking of nanocarriers.

Acknowledgements

Adapted from Witzigmann et al.⁵ with permission from The Royal Society of Chemistry. Financial support of the “Stiftung zur Förderung des pharmazeutischen Nachwuchses” in Basel is acknowledged. In addition, we thank Prof. Henning Stahlberg (Director, Centre for Cellular Imaging and NanoAnalytics [C-CINA]) for his support.

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2016 Allan Hoffman Student Travel Grant Program



Allan S. Hoffman is a true pioneer in the fields of polymer chemistry, biomaterials, drug delivery, and diagnostics. He has been actively involved in research for well over 50 years and has made numerous contributions to our field. Dr. Hoffman has been recognized with numerous awards throughout his distinguished career, including the CRS Founder's Award in 2007, and he was inducted into the CRS College of Fellows in 2010. Therefore, CRS is honoring Allan Hoffman via funding student travel awards so promising young scientists can attend the 2016 CRS Annual Meeting.

The CRS Foundation Board has selected Dr. Hoffman to be honored for his achievements and his leadership at the 2016 annual meeting of the society to be held in Seattle, Washington, on July 17–20. The goal is to provide an opportunity for those individuals who have gained personal and professional benefit from his work and leadership to express their gratitude. Thus, it is extremely fitting that CRS now wishes to honor him through the funding of student travel awards. At this time, the CRS Foundation is requesting donations to fund these travel awards and allow the next generation of CRS leaders to meet and learn from Dr. Hoffman. Learn more at controlledreleasesociety.org/about/foundation/Pages/StudentTravelGrants.aspx. ■



"I think the most important attributes for a scientist are curiosity and a desire to learn new things. I like to listen and talk with people about their research. I try to learn something new every day, which is the key to expanding my mind and having more fun with science."

– Allan Hoffman

Drug Delivery Australia

Rachel Stephenson, University of Queensland, Australia

Drug Delivery Australia (DDA) 2015, “Recent Advances in Drug Delivery Technology” was the 9th annual meeting of the CRS Australian Local Chapter, held on November 19 and 20 at St. Leo’s College, University of Queensland in Brisbane. The meeting comprised invited and contributed talks and posters from a range of fields of delivery research, including pulmonary delivery, anticancer drug delivery, gene and siRNA delivery, and polymer-based delivery platforms, from both academic and industry speakers. The conference provided a platform for showcasing a variety of research toward improving drug delivery across Australia and New Zealand. This year we hosted 99 visitors from the United Kingdom, Malaysia, India, New Zealand, and all over Australia.



DDA 2015 had an emphasis on advanced delivery systems, and this was evident from the two plenary speakers. Yvonne Perrie (Aston University, United Kingdom)—an editor of the *CRS Newsletter* who was recently a director-at-large for CRS and is a past chair for the United Kingdom–Ireland CRS Local Chapter—gave an insightful plenary talk. On the second day, Mohd Cairul Iqbal Mohd Amin (Universiti Kebangsaan, Malaysia) gave an interesting overview on smart hydrogels for oral delivery of protein-based drugs. Through this meeting, we aimed to form stronger ties with the CRS Malaysian Local Chapter, where Cairul is the president.

The conference commenced with an opening address from Paul Young, head of the School of Chemistry and Molecular Biosciences at the University of Queensland, followed by our first plenary speaker, Yvonne Perrie, giving her presentation entitled “Liposomal Adjuvants—Harnessing Drug Delivery to Improve Vaccine Efficacy.” There were four talks presented in the following session on oral delivery. Timothy Barnes (University of South Australia) described his research on multi-compartmental oral vaccine delivery systems. Continuing the oral delivery theme, Shasha Rao (Ian Wark Research Institute) presented a polymer and silica-lipid hybrid for improving oral delivery of poorly water-soluble drugs. A stimuli responsive nanoparticle for oral delivery was described by Clive Prestidge (University of South Australia), while Amirali Popat (University of Queensland) ended the session with an interesting talk on stimuli responsive nanoparticles for oral delivery.



Opening address and welcome by Paul Young.



Plenary speaker Yvonne Perrie.

The afternoon started with a session on cancer delivery. The first speaker, Richard Williams (RMIT University), presented research on nanogels. His talk was followed by Sarah Hook (University of Otago, New Zealand) on targeted cancer therapeutics and Sanyog Jain (NIPER, India) on nanotechnology intervention for cancer chemotherapy. Ending the session, Thomas Haselhorst (Griffith University) gave a motivating talk on targeted immune-glycotherapy for the treatment of non-Hodgkin’s lymphoma.

After a welcome afternoon tea break to enjoy the warm sunshine Brisbane had on offer, the last session of the day focused on advanced formulations. The first speaker, Simone Flight (Clinical Network Services) presented an industrial talk on topical drug formulations—regulatory and real world. Her talk was followed by Daniela Traini (University of Sydney) on novel targeted drug delivery to the lung. Christoph Hagemeyer (Baker IDI Heart and Diabetes Institute) spoke about preventing unstable plaque ruptures using targeted nano-drug delivery to increase plaque fibrous collagen via matrix metalloproteinase inhibition. This was followed by an interesting talk by Bijun Zeng (University of Queensland) on targeting dendritic cell receptors using nano-emulsions.



Plenary speaker Mohd Cairul Iqbal Mohd Amin.

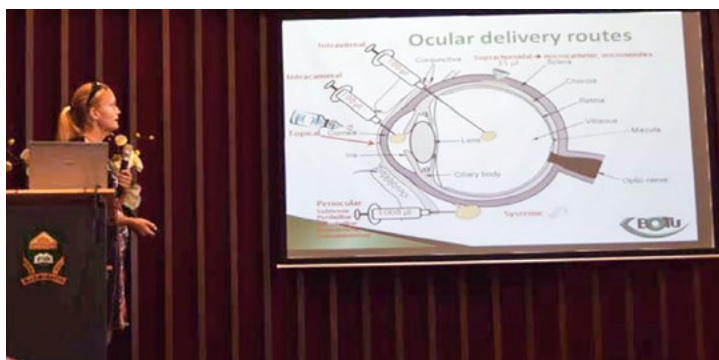
The second day of the DDA 2015 conference started with a thought-provoking plenary talk from Mohd Cairul Iqbal Mohd Amin. Cairul gave an overview of smart hydrogels for oral delivery of protein-based drugs. This session was followed by the highly anticipated Rapid Fire Talks (three minutes each) by eight Ph.D. students, preselected the day before from their posters. The students did an excellent job keeping to time, and the presentations were all short,

entertaining, and a real pleasure to listen to. The winners of the two \$1,000 cash contributions to attend the next CRS conference in Seattle, WA, U.S.A., in 2016 were Khairul Azfar Kamaruzamam (University of Queensland) and Nicole Bisset (Monash Institute of Pharmaceutical Sciences). The \$200 eBook voucher was awarded to Sharan Bobbala (Otago University, New Zealand).

The session on oligonucleotide and polymer delivery started with an exciting talk from Michael Monteiro (University of Queensland) on polymers in biomedical applications. The session continued with Peter Moyle (University of Queensland) talking about optimising delivery systems for the transport of oligonucleotides and Markus Mullner (University of Sydney) on the design of cylindrical polymer brushes. Paul Young (University of Sydney) gave an interesting talk on the complex delivery of particles to the lung. Lastly, in this session, Kara Vine (University of Wollongong) gave an insightful presentation on degradable polymeric fibres for the treatment of pancreatic cancers.



The top eight poster presentations by students preparing to give their Rapid Fire Talks.



Ilva Rupenthal's presentation on ocular delivery.

Following lunch, the session on recent advances in drug delivery started with Ilva Rupenthal (University of Auckland, New Zealand), who gave a motivating talk on stimuli-responsive implants for drug delivery to the posterior segment of the eye. Her talk was followed by Ian Tucker (Otago University, New Zealand) with his work on the challenges in oil-based delivery systems for veterinary applications. We also learned a lot about how “oils aren’t oils” with respect to the motor sport industry! Nhung Dang (University of Queensland) gave an insightful talk on treating skin diseases using microparticle technology, and Nam-Trung Nguyen (Griffith University) followed the theme with his talk on liquid marbles and three-dimensional cell culture. Lastly, Makrina Totsika (Queensland University of

Technology) informed us about novel anti-microbial approaches for multi-drug resistant pathogens.

The last session of the conference focused on targeted delivery systems. Nazrul Islam (University of Technology) started with a talk on the controlled release of drugs from polymeric nanoparticles. Arlene McDowell (Otago University, New Zealand) followed with insight into the nano-bio interface to optimise a drug dose. Last but not least, Michael Crichton (University of Queensland) concluded the DDA 2015 conference with a talk on delivering solid vaccine formulations to epithelial tissues using micro-projection arrays.

The conference dinner, sponsored by Davies Collison Cave, was held at the Shore Restaurant, Southbank, in the heart of Brisbane, where an excellent meal was had along with spectacular views of Brisbane.

The meeting was strongly supported by our sponsors: the University of Queensland School of Chemistry and Molecular Biosciences, CRS, ThermoFisher Scientific, TrendBio, Sigma-Aldrich, CNS, Davies Collison Cave, the Woolcock Institute of Medical Research, Monash Institute of Pharmaceutical Sciences, and Interpath Services. We extend our thanks for their generous and continued support.

This highly informative and efficient two-day meeting was a great success, with a number of collaborations arising from discussions and networking, as well as great exposure for the students involved. The quality of the meeting was again testament to the growing significance of drug delivery research across Australia. Plans for the next meeting in Sydney in October/November of 2016 are already underway. ■



The conference dinner at the Shore Restaurant.

Rheology: How to Get into the Flow

Sarah Streck and Sasi Bhushan Yarragudi, School of Pharmacy, University of Otago, New Zealand

November 24, 2015, was a day of rheology at the School of Pharmacy, University of Otago, Dunedin, when the invited speakers and 35 participants came together for the combined workshop of the New Zealand and Australian CRS chapters, “Pharmaceutical Rheology—Principles and Applications.” With this workshop we entered the world of rheology and got information, ideas, and advice to find our own way through the complexity of the topic.

Rheology describes the flow of a wide range of materials and accompanies us through the day, every day. In the morning we first get in contact with the flow of materials when we enter the bathroom and use shower gel, shampoo, and toothpaste. Later at work we continue with gels, polymers, and excipients, and finally rheology finds its glorious ending when we add ketchup to our fries for dinner.

Ph.D. students Sharan Bobbala and Sasi Bhushan Yarragudi welcomed all the invited speakers and participants from the University of Otago and the University of Auckland. Greg Walker (University of Otago), the vice president of NZCRS, opened the workshop, explaining the meeting was dedicated to everyone getting a better understanding of rheology.

The first speaker was Stefania Baldurdottir (University of Copenhagen, Denmark). After her long travel from Europe to New Zealand, she polished up our knowledge about rheology and highlighted some important basic rules and how to deal with them in the lab. In her talk she also shed light on the analysis and logical interpretation of data obtained from rheology studies.

Our next speaker, Natalie Medlicott (School of Pharmacy, University of Otago) focused on the pharmaceutical application of rheology, and her target site was the “periodontal pocket as a consequence of periodontal disease,” as well as the investigation of salvia. She emphasized the importance of rheology and its measurements in development of a successful pharmaceutical formulation.

The lunch break with a variety of good food was the first opportunity for participants and speakers to discuss the first talks of the day.



Patrick Spicer (Photo by Arlene McDowell)

Patrick Spicer (University of New South Wales, Australia) was the first speaker in the second session. In his passionate talk, “Microstructure and Rheology of Complex Fluids,” he focused on application of rheology measurements to interpret microstructure and the challenges with small volume rheology. He also gave us a lot of daily examples and provided tips for hair care.

The next speaker, Steve Moratti (Department of Chemistry, University of Otago), explained the importance of rheology measurements to measure properties of gels and how gels can be used in surgery. Furthermore, he produced a gel in front of us as a practical example.

continued

FEEDBACK FROM PARTICIPANTS

“I really enjoyed the Rheology workshop. As someone who was new to this technique this workshop provided me with a good insight into the verticality of this technology and helped me understand how to interpret the data obtained.”

Blake Gibson, Laboratory Technician, School of Pharmacy, University of Otago

“For me, the rheology workshop is an extremely useful workshop. I can get more academic knowledge and practical experience from an academic speaker. It is a good chance for me to discuss with others, both academic and student.”

Hanh Vu, Ph.D. student, School of Pharmacy, University of Otago

“I really enjoyed the rheology workshop. It was well organized with both theoretical and practical training sessions. Moreover, the speakers’ personal experiences and their recommendation to eliminate the possible problem with experimentation are very useful. Overall it is one of the best workshops which I have attended.”

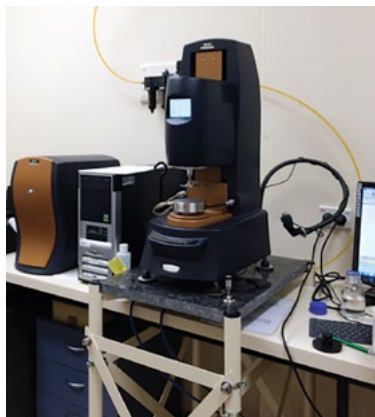
Basanth Eedara, Ph.D. student, School of Pharmacy, University of Otago

“This workshop was really worth the visit. At my home university we had already very extensive lectures about rheology, but this workshop was a welcome refresher and much more practically orientated than those lectures could ever be.”

Robert Richter, visiting researcher, Free University of Berlin, Germany

The next point on the programme was the practical session using the rheometer. This was a great opportunity to get in contact with the invited speakers, and a good conversation between speakers and participants started immediately.

Sharan Bobbala showed us the new HR-3 oscillatory rheometer and explained step by step how to use the instrument and software. Also, he acquainted us with details and tricks to make us feel more confident for our further work with the rheometer. After both groups saw the practical demonstration on the rheometer we continued the conversations with the speakers during the afternoon tea.



The HR-3 oscillatory rheometer during the practical demonstration. (Photo by Sarah Streck.)

To complete the programme, two Ph.D. students shared their experiences with the work on the rheometer and their tricks for its efficient use. Sharan Bobbala (School of Pharmacy, University of Otago) started with his talk about the “Characterization of Thermoresponsive Hydrogels.” The contents of the talk reflect what Sharan did during his Ph.D., and we are looking forward with him to his graduation in December. The second talk was given by Prabhat Bhusal (University of Auckland). Prabhat is in his second year of Ph.D. study and showed us the results he found about “The Rheology of Biological Fluid,” such as synovial and peritoneal fluids.

Finally, Natalie Medlicott thanked everyone for coming, speaking, and participating. It was a great day, and the good organisation made it easy to get in contact with the invited speakers. All participants learned more about the wide and interesting field of rheology. ■



Stefania Baldurdottir, who presented a talk entitled “Rheology 101,” donned Otago Ph.D. regalia to join in the graduation fun during her trip to Dunedin. (Photo by Natalie Medlicott.)

Micro- and Nanotechnologies to Overcome Biological Barriers: Eighth Annual CRS Italy Local Chapter Workshop

Pietro Matricardi¹ and Giuseppe De Rosa²



The workshop was held at the University of Naples Federico II.

The CRS Italy Local Chapter annual workshop, “Micro and Nanotechnologies to Overcome Biological Barriers,” was held in Naples on November 12–14, 2015, and more than 140 delegates attended this important meeting. The meeting was held in the comfortable building of the Ex-Facoltà di Scienze Biotecnologiche, University of Naples Federico II.

Before the official start of the meeting, a morning session was held specifically dedicated to Ph.D. students and postdocs. The topic of this session was “Liposomes in Drug Delivery: From Basics to Clinical Applications.” The outstanding scientists Elias Fattal (Université Paris-Sud, France) and Gert Storm (Utrecht University, the Netherlands) held this “school on liposomes” in a friendly and communicative way. All 35 attendees were enthusiastic about the clarity of the expositions and the knowledge transfer.

The workshop started with a welcome from the president of the CRS Italy Local Chapter, Bice Conti (University of Pavia), and Giuseppe De Rosa, president of the local organizing committee. In her introduction, Bice Conti reminded everyone of the goals of CRS and upcoming activities. In particular, she underlined the relevance of the CRS Italy Local Chapter annual meeting for the Italian drug delivery community. Moreover, the importance of the meeting was highlighted by the presence of award-winning European scientists working in our field.

The workshop was structured following a consolidated form to favour open discussion, brainstorming, and information exchange among the participants. The meeting was divided into four sessions, including 15 speakers who gave 40 minute main lectures followed by 20 minute discussions, which were chaired and directed by discussant panels of scientists. Among the various lectures, some short technical communications were given by the sponsors of the meeting; their contributions were extremely important for the success of the meeting.

The lecture “Innovative Delivery Approaches in the Era of Microenvironment Targeted Anticancer Treatment” from Pierosandro Tagliaferri (Università degli Studi Magna Graecia of Catanzaro) opened the scientific session, giving the audience a different point of view on innovative approaches for cancer treatment. This lecture warmed up the floor and excellently introduced the theme of the workshop.

The first session, “Biomaterials,” was opened by the second invited lecturer, Tal Dvir (Tel Aviv University, Israel), entitled “Engineering Strategies for Regenerating the Diseased Heart,” which described cutting-edge technologies for engineering functional cardiac tissues or releasing biofactors.

The next talk was delivered by Gert Storm and was focussed on theranostic strategies for monitoring and optimising targeted nanomedicines. His presentation was engaging, stimulating discussion in the audience.

The last communication of the session was entrusted to Margherita Morpurgo (Padua University), who described her recent results on “Antibody Guided Nanoparticles Versus Antibody Drug Conjugates: A Quantitative Approach for Cell Trafficking and Potency Comparisons Using the Avidin Nucleic Acid Nano System (ANANAS) Technology.”

The second session of the meeting focussed on “Drug Targeting/Theranostics” and was opened by Paolo Antonio Netti (IIT, Naples) presenting some results on the polymeric nanoshuttles for theranostic applications developed in his laboratory. The second speaker of the session was Mirco Ponzoni (G. Gaslini Institute, Genoa). His talk was focussed on the “tumour vascular targeted approach” in overcoming biologic barriers for the therapy of neuroblastoma. He fascinated the audience, presenting exciting and promising data on this aggressive tumour in children.

The following speaker, Luisa Fiandra (University of Milan), illustrated how “Nanoformulation of Antiretroviral Drugs Allows Their Release over the Blood Brain Barrier: *In Vitro* and *In Vivo* Assays,” and Armando Cevenini (University of Naples Federico II) concluded the second session by reporting on “Tools and Avenues for Nanotechnology-Based Vectors Exploitation for Biomarker Signature and Therapeutical Drug Delivery.”

¹ University “La Sapienza” of Rome, Italy.

² University of Naples Federico II, Italy.



Ijeoma Uchegbu presents on nanotechnology.



Arto Urtti presents on ocular drug delivery systems.



Andreas Bernkop-Schnürch presents on strategies to overcome the mucus gel barrier.

The third session was specifically dedicated to “Drug Delivery to the Brain.” The first presentation was given by Ijeoma Uchegbu (University College London, United Kingdom). During her presentation, entitled “Exploiting Nanotechnology to Create New Medicines—The Journey So Far,” she retraced the long and hard process of developing new drug delivery systems for delivering peptides into the brain to fight many important brain diseases. In particular, she underlined the main tasks that should be overcome and the

strategies that can be adopted to reach this important goal. The second invited speaker of the session, Sophia Antimisiaris (University of Patras, Greece), updated the audience on “Multifunctional Nanoliposomes for Targeting Amyloid Deposits in the Brain,” showing the feasibility of nanoliposomes decoration with two ligands to target the brain and amyloid species as potential theranostic systems for this brain disease in *in vitro* and *in vivo* performances.

Massimo Masserini (University Bicocca of Milan) reported on his recent work on “Functionalization of Nanoparticles with Plasma Proteins as a Strategy to Cross the Blood-Brain Barrier.” This exciting and hard work suggests that physiological circulating proteins in plasma can be exploited to devise new strategies to efficiently drive nanoparticles across the blood-brain barrier.

Finally, Giovanni Tosi (Modena Reggio Emilia University) reported, in an unusual and fascinating way, the results of his group on “Nanomedicine: Overcoming Blood-Brain Barrier with Nanoparticles,” using polymeric nanoparticles decorated with various ligands. The last day started with the fourth session of the meeting, “Topical/Mucosal Delivery.” Arto Urtti (University of Helsinki, Finland) illustrated his research experience on “Pharmacokinetic Factors in the Design of Ocular Drug Delivery Systems.” In detail, he presented some models that can be used in predicting and simulating the pharmacokinetics and drug delivery to ocular targets after drug administration, according to the various routes of administration.

Francesca Maestrelli (University of Florence) gave a presentation on “Metformine HCl-Loaded Chitosomes and Niosomes: *In Vivo* Studies of Hypoglycaemic Effect.” She evidenced, in his research, that the therapeutic efficacy of metformine is improved using an appropriate drug delivery system.

The wide data set presented by Andreas Bernkop-Schnürch (University of Innsbruck, Austria) in his talk entitled “Micro- and Nanocarriers: Strategies to Overcome the Mucus Gel Barrier” gave the audience an important overview on approaches that can be exploited in overcoming this important biological barrier. His presentation concluded the session and the scientific contributions.

The workshop included a poster session with contributions. This year, three posters were awarded. The first award, an *ex aequo*, was selected by a committee composed by the invited speakers, while the second prize was selected by the vote of all delegates.

The workshop was closed by Elias Fattal with concluding remarks. The workshop program was a great success, and the contributions of invited speakers were extremely appreciated by participants because they did not limit themselves to presenting their research but were actively involved in the critical open-minded discussion that opened novel viewpoints on research.

Social activities included a welcome cocktail and social dinner, which were attended by all delegates. These important events were appreciated, as they help networking.

The workshop was supported by CRS and generously sponsored by QI Technologies, Evonik, Lipoid, Capsugel, Alfatest, MP instruments, Pharma D/S, Jasco Europe, polycrystalline, Eppendorf, Avantech, Grace, Nordtest, and Harke. The associations Federfarma, Ordine dei Farmacisti della provincia di Napoli, and the Ordine dei Farmacisti della provincia di Avellino contributed to the meeting organization.

All abstracts are available on the website of the CRS Italy Local Chapter, www.itcrs.it/itcrs2. ■



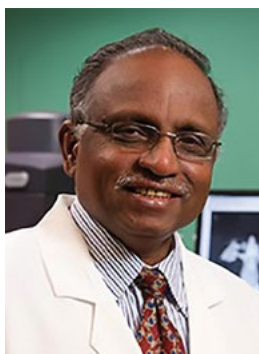
The poster awards ceremony.



The social dinner in a typical Neapolitan restaurant.

Drug Delivery and Translational Research Update

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



Vinod Labhasetwar

DDTR Now Published by Springer Nature

In 2011, Springer Science+Business Media launched *Drug Delivery and Translational Research* (DDTR), an official journal of the Controlled Release Society. In a 2015 merger, through the combination of Nature Publishing Group, Palgrave Macmillan, Macmillan Education, and Springer Science+Business Media, the newly formed Springer Nature will continue to publish DDTR on Springer's online platform SpringerLink, including Online First™, cross reference linking, and alert services. The journal will be provided to all CRS members as a benefit of membership. Visit the CRS website for instructions to access the articles published in DDTR.

Springer Nature is a major new force in scientific, scholarly, professional, and educational publishing with a global footprint. Using a unified-company approach, Springer Nature provides quality content that will further the CRS initiative to communicate the incredible

growth and advances in drug delivery science and technology. This strategic merger brought together these dynamic publishing houses with more than 150 years of history behind them, as well as complementary geographic footprints and brand portfolios, a track record of creativity and innovation, and a shared vision to advance knowledge and learning around the world. The company numbers almost 13,000 staff in over 50 countries and has a turnover of €1.5 billion. DDTR will reach an ever-growing multidisciplinary audience whose work centralizes on improving drug delivery systems and optimizing the bioavailability of drug products for disease conditions.

Upcoming Special Issue: Orthopedic Biomaterials and Drug Delivery

The issue will showcase emerging pharmaceutical and regenerative approaches to treat injuries, diseases, and disorders of the musculoskeletal system. Topics included are gene/drug delivery systems, cell-based therapies, and biomaterials to support orthopedic tissue regeneration and/or disease modification. Guest editors: Blanka Sharma (blanka.sharma@bme.ufl.edu) and Shyni Varghese (svarghese@eng.ucsd.edu).

DDTR Special Issue Under Development: Ocular Drug Delivery

DDTR is accepting submissions for a special issue on ocular drug delivery, which will showcase emerging pharmaceutical, engineering, and formulation approaches to efficiently treat both anterior and posterior segment diseases. Topics include topical formulations, ocular implants, and other delivery systems for both small and large molecules, including proteins and genes, with a focus on their application in disease conditions including preclinical and clinical data. Emphasis will be placed on ocular pharmacokinetics as well as short- and long-term ocular biocompatibility with a focus on clinical translation, new product development, and market opportunity. Guest editors: Ilva Rupenthal (i.rupenthal@auckland.ac.nz) and Michael O'Rourke (scotiavc@gmail.com).

DDTR Outstanding Research Paper Award

It is time to consider submitting your best research for the 2016 DDTR Outstanding Research Paper Award. The paper will be selected from the research articles, clinical research, and clinical trials published in DDTR during 2016. The award will be presented during the 44th CRS annual meeting, to be held July 16–19, 2017, at Hynes Conventional Center, Boston, Massachusetts, U.S.A. Visit the CRS website for award criteria.

DDTR Download Data

We are marching toward the landmark of 100,000 total downloads. We anticipate that DDTR will reach that mark sometime in 2017. Articles published in DDTR average an impressive 250 downloads.

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2013	16,047
2012	9,654
2011	5,609
Total downloads	67,287
Downloads per article	~250

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Drug Deliv. Transl. Res. 1(3): 209-222
www.ncbi.nlm.nih.gov/pubmed/22708075

Convection-enhanced delivery of camptothecin-loaded polymer nanoparticles for treatment of intracranial tumors

Andrew J. Sawyer, Jennifer K. Saucier-Sawyer, Carmen J. Booth, Jie Liu, Toral Patel, Joseph M. Piepmeier, and W. Mark Saltzman
Drug Deliv. Transl. Res. 1(1): 34-42
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Nasal drug delivery devices: Characteristics and performance in a clinical perspective—A review

Per Gisle Djupesland
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www.ncbi.nlm.nih.gov/pubmed/23316447

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Drug Deliv. Transl. Res. 1(6): 409-419
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Strategies for intranasal delivery of vaccines

Mehfuz Zaman, Saranya Chandrudu, and Istvan Toth
Drug Deliv. Transl. Res. 3(1): 100-109
www.ncbi.nlm.nih.gov/pmc/articles/PMC3539070 ■

People in the News

Compiled by Steven Giannos, Independent Consultant

PixarBio Cofounder Robert S. Langer Awarded the 2016 Benjamin Franklin Medal in Life Science for His Excellence in the Field of Tissue Engineering

Business Wire, November 16, 2015 – CAMBRIDGE, MA, U.S.A. – PixarBio Corporation is proud to announce that our cofounder Robert S. Langer was named the recipient of the 2016 Benjamin Franklin Medal in Life Sciences from the Franklin Institute of Philadelphia to be awarded on Thursday April 21, 2016.

The long, distinguished history of The Franklin Institute awards program dates back to 1824, when the institute was founded by a group of leading Philadelphians to train artisans and mechanics in the fundamentals of science. Philadelphia, then the largest city in the United States, was a burgeoning manufacturing center. In 1824, the institute arranged the first of a series of annual exhibitions of manufactured goods. With these exhibitions came the presentation of awards—first certificates, and later endowed medals—for achievements in science and invention. The first written record of the awards is in volume 1, number 1 of the *Journal of The Franklin Institute* published in January 1826.

Through its awards program, The Franklin Institute seeks to provide public recognition and encouragement of excellence in science and technology. The list of Franklin Institute laureates reads like a “Who’s Who” in the history of 19th, 20th, and 21st century science, including Nikola Tesla, Thomas Edison, Rudolf Diesel, Pierre and Marie Curie, Orville Wright, Albert Einstein, Edwin Hubble, Frank Lloyd Wright, Edmund Bacon, Marshall Warren Nirenberg, Jacques Cousteau, Mildred Cohn, Stephen Hawking, Martin Rees, Paul Baran, Gordon Moore, Jane Goodall, Herb Kelleher, Elizabeth Blackburn, Bill Gates, Dean Kamen, Subra Suresh, and Michael Dell.

Robert S. Langer was awarded the Franklin Medal in Life Science for his design and implementation of multiple innovative drug delivery systems, and for his founding work in the field of tissue engineering. As the leader of the world’s largest academic research lab and a serial entrepreneur, Dr. Langer established a new paradigm for translating academic ideas into practical U.S. FDA approved products.

“For 191 years the Franklin Institute has provided inquisitive minds of all ages, a deep exploration into the sciences and technology. As a scientist and engineer Bob Langer’s medical inventions have impacted over two billion lives. On a daily basis Bob opens new doors for both patients and scientists as he engages some of the most challenging neurological conditions, and Bob’s impact will last for centuries. It’s an honor for our team to work with Bob as we extend just a couple of the fields he cofounded, tissue engineering and drug delivery, into chronic neurological disease,” said PixarBio CEO Frank Reynolds.

Cofounded by Frank Reynolds, MIT’s Robert S. Langer, Katrin Holzhaus, and Jason Criscione, PixarBio is focused on researching and developing targeted delivery systems to treat pain, epilepsy, Parkinson’s disease, and spinal cord injury. For more information, visit www.pixarbio.com. ■

Companies in the News

Compiled by Steven Giannos, Independent Consultant

January

Phosphagenics Reports Positive Results for Weaner Pig Feed Efficiency Trial

Business Wire: January 20, 2016 – MELBOURNE, Australia – Australian drug delivery company Phosphagenics Limited (ASX: POH; OTCQX: PPGNY) is pleased to report positive results in its initial animal health and nutrition trial. This trial, in more than 1,500 weaner (young) pigs, is the first in a series of planned randomized, controlled studies designed to assess if TPM® can enhance the efficiency in which livestock converts feed into weight gain (measured as feed conversion ratio [FCR]).

The study compared the benefit of TPM® at doses of 5–40 mg/kg with that of increasing doses of vitamin E (dl-alpha-tocopherol acetate) up to 160 mg/kg across the first two development phases post weaning (phase 1: 0–14 days, and phase 2: 15–34 days). Weaner pigs are subjected to significant metabolic stress due to high growth rates, change of diet, and social stress, which can result in significant production limitations, particularly during the first of these phases. It is believed that supporting pigs at this early stage of the commercial lifecycle provides the opportunity for maximum growth potential long-term, conferring a potentially significant financial benefit to farmers and the food industry.

In the first phase (0–14 days), TPM® treatment resulted in a statistically significant, linear dose-dependent improvement in feed efficiency. The FCR with 40 mg/kg of TPM® was >3% better than the best result achieved with any dose of vitamin E. The potential for further improvement in FCR exists at higher doses of TPM® than used in the current study.

The significant difference observed in the first phase of the trial was not seen in the second phase (days 15–34 of treatment). Unforeseen health issues in the pigs during this second phase resulted in significant suppression of performance across the board for all treatment groups, compromising FCR assessments.

The general manager of Phosphagenics' animal health and nutrition business, Dr. Roksan Libinaki, said, "The first few weeks postweaning are seen as a critical period in which production limitations can occur for the pork industry. It is very pleasing to see that, despite some challenges in the study, we were still able to demonstrate that TPM® can provide a significant benefit in the form of improved FCR during this important phase of development. Achieving an improvement in feed efficiency of greater than 3% at this weaner stage provides a good platform to substantiate the potential benefits of TPM® as a feed additive. We see these results as important in positively differentiating the potential of TPM® in the minds of our potential partners across multiple species."

Phosphagenics' CEO, Dr. Ross Murdoch, said, "This is an important result for our animal health and nutrition business and supports further investment in our TPM® livestock feed additive program. This study provides compelling data to present to major feed producers with a view to entering partnering arrangements. The next grower/finisher pig study will provide further means to assess the potential value of TPM®'s applications in pigs.

Additional studies are planned for production animals throughout 2016, to assess the value of TPM® across the broader market segment. The grower/finisher pig study is on track to be completed in Q2 2016.

Ensysce Biosciences Inc. and Signature Therapeutics Inc. Merger

Business Wire: January 19, 2016 – SAN DIEGO, CA, U.S.A. – Ensysce Biosciences and Signature Therapeutics are pleased to announce completion of a formal merger on December 31, 2015, naming Dr. Lynn Kirkpatrick as CEO. The company will retain the name of Ensysce Biosciences and will be relocating to San Diego, California. Ensysce becomes an integrated drug delivery company for both small and large molecules. The small molecule focus is developing abuse and overdose resistant pain technology with a clinical program ready to launch for the lead abuse resistant, BIO-MDTM opioid product, PF614. The Ensysce delivery platform for large biomolecules is utilizing single walled carbon nanotubes (SWCNT) to produce intravenously delivered immunology and gene therapy products.

Dr. Bob Gower and William H. C. Chang, both chairmen of the respective companies, join the board of the combined company with Dr. Gower becoming chairman of the board. Dr. Gower, founder of Ensysce and former president and CEO of Carbon Nanotechnologies Inc., which he founded with the late Nobel Prize winner Dr. Richard Smalley, has more than 40 years of

continued

experience in the chemical industry with Atlantic Richfield, ARCO Chemical, and Lyondell Petrochemical. William Chang, the chairman of Westlake International Group, a privately held, diversified investment company with operations in the United States, China, Japan, and India, is also the co-owner of the San Francisco Giants baseball club and D.C. United of the MLS, and chairman of the executive committee of USA Rugby.

“This merger provides the opportunity to tackle some of the most challenging delivery problems in the pain and oncology fields,” said Dr. Kirkpatrick. “We now have the ability to provide pain medicine that eliminates the potential for abuse with our BIO-MDTM oral prodrug technology and our overdose resistant MPARTM products. The near term clinical trials for the pain products will complement our SWCNT platform that has demonstrated ability to transfect circulating T-cells following intravenous administration. An IV product could transform manufacturing procedures of the highly promising immunotherapy and gene editing technologies. I am delighted to be playing a role in the development of these transformative technologies.”

Ensysce, founded in Houston, Texas, has an extensive carbon nanotube-related, worldwide intellectual property portfolio, including IP developed at Rice University by Dr. Smalley, at the University of Florida and Trinity College in Dublin, and issued patents of Ensysce for the use of SWCNT for therapeutic applications.

Signature, from Palo Alto, California, focused on novel chemical entities for treatment of pain and neurological disorders. Their BIO-MDTM platform eliminates the ability to abuse opioid products by the non-oral route, something that is the fastest growing drug problem in the United States and that leads to billions in healthcare costs annually.

Evestra Receives Gates Foundation Grant

Business Wire: January 18, 2016 – SAN ANTONIO, TX, U.S.A. – Evestra, Inc., has received a grant from the Bill & Melinda Gates Foundation to advance research on a technology that could lead to long-acting injectable fertility control for women in underserved regions such as sub-Saharan Africa, where less than 20% of women use modern fertility control.

“We share the Gates Foundation’s concern that more than 220 million women who don’t want to get pregnant and who live in developing countries lack access to fertility control and voluntary family planning information and services,” said Ze’ev Shaked, Ph.D., Evestra’s president and CEO. “We applaud the foundation’s commitment to solving this problem. Evestra’s expertise and innovative approach to women’s health issues will greatly benefit the Gates Foundation’s efforts. We’re excited to work with them.”

Evestra is applying its proprietary prodrug platform technology to the development of the product, said Klaus Nickisch, Ph.D., Evestra’s chief scientific officer. A prodrug is a compound that is inactive until it is inside a human body, where metabolic processes convert it into an active drug.

Evestra Inc. (www.Evestra.com) is a San Antonio, Texas-based biopharmaceutical company engaged in the research and development of innovative women’s healthcare products. Evestra’s products address unmet medical needs in women’s health arenas and are derived from three research platforms—steroidal medicinal chemistry, vaginal drug delivery, and prodrug technology.

Heron Therapeutics Notified by FDA That It Will Not Take Action on SUSTOL® New Drug Application by the PDUFA Date

Business Wire: January 15, 2016 – REDWOOD CITY, CA, U.S.A. – Heron Therapeutics, Inc. (NASDAQ: HRTX), announced today that the U.S. Food and Drug Administration (FDA) has informed the company that it has not yet completed its review of the New Drug Application (NDA) of SUSTOL® (granisetron) injection, extended release and would not be taking action by the Prescription Drug User Fee Act (PDUFA) goal date of January 17, 2016, and anticipates taking action in late February 2016.

SUSTOL is a long-acting formulation of the FDA-approved 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist granisetron being developed for the prevention of both acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC). SUSTOL is formulated utilizing Heron’s proprietary Biochronomer® drug delivery technology and has been shown to maintain therapeutic drug levels of granisetron for at least five days with a single subcutaneous injection.

Heron Therapeutics, Inc., is a 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. Heron’s goal is to build on therapeutics with well-known pharmacology by improving their tolerability and efficacy as well as broadening their potential field of use. For more information, visit www.heronrx.com.

Neutra Corp. Explores Promising Cannabinoid Treatments for Chronic Migraines

Business Wire: January 14, 2016 – TAMPA, FL, U.S.A. – As mounting evidence suggests that the administration of cannabis can reduce the frequency of migraine headaches, Neutra Corp. (OTCQB: NTRR) will explore the promise of advanced cannabinoid delivery technologies to ease migraine sufferers' pain.

Data published online ahead of print in the journal *Pharmacotherapy* finds that cannabis administration is clearly associated with decreased migraine frequency. The report comes from investigators at the University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences, who assessed cannabis's effects on monthly migraine frequency in a group of 121 adults. The authors discovered that 85% of subjects reported a decrease in migraine frequency, with 12% reporting that use of cannabis prior to a migraine's onset could prevent a headache altogether.

Case reports have previously documented positive results for cannabis in the treatment of migraines, leading scientists to theorize that cannabinoids may have a role to play in migraine regulation.

NTRR is working to devise new cannabinoid delivery technologies in order to help medical cannabis patients treat their migraines more reliably and effectively. In its quest to build a portfolio of wellness-related technology assets ripe for commercialization, NTRR is researching cutting-edge cannabis inhaler technology, as well as a range of cannabis-infused topicals to potentially include lotions, oils, and balms.

"Cannabis is used to effectively treat all sorts of maladies, so it only makes sense that consumers are demanding a wide variety of compatible drug delivery methods," said NTRR CEO Chris Brown. "Inhalers and topical salves could provide superior options to patients suffering from migraines and debilitating issues."

Neutra Corp. is a healthy lifestyle company that specializes in the development and marketing of natural wellness solutions, including cannabis-related products. By providing a variety of new technologies designed to ensure safer, more reliable access to cannabis in approved markets, Neutra Corp. plans to compete alongside GW Pharmaceuticals (OTCBB: GWPRF), INSYS Therapeutics, Inc. (NASDAQ: INSY), and ENDEXX Corp. (OTCBB: EDXC), delivering technological advancements in the cultivation and processing of cannabis in approved markets. For investing information and performance data, please visit www.neutracorp.com.

SynCore Biotechnology to Present EndoTAG™ Technology Platform and Its Breakthrough Product EndoTAG™-1 and Novel Anticancer Drug Candidate SB01 at Biotech Showcase™ 2016

PRNewswire: January 8, 2016 – TAIPEI CITY, Taiwan – A new drug platform and product development biotechnology company is developing a new drug platform for potential cancer treatment and managing the oncology products at clinical stage.

EndoTAG™ technology platform is a novel, cationic liposomal technology that targets vascular endothelial cells in regenerated blood vessels that carry negative electric charges within the tumor. Different from the other liposomal-embedded drug delivery systems that directly only target the cancer cells, EndoTAG™ destroys cancerous cells through anti-angiogenesis.

EndoTAG™-1, a synergistic product of an innovative composition of the established cytotoxic drug paclitaxel combined with EndoTAG™ technology, interacts with newly formed, negatively charged endothelial cells, which are specifically required for the growth of tumor blood vessels. It attacks the activated endothelial cells as they divide; thus, EndoTAG™-1 only targets the blood supply to tumors but does not affect healthy tissues. EndoTAG™-1 is expected to prevent the formation of new tumor blood vessels and to inhibit tumor growth.

SB01 is an injectable formulation of a novel heterocyclic combretastatin A-4 (CA-4) analogue drug candidate that inhibits tubulin polymerization through binding to the colchicine-binding site of tubulin. It mostly exhibits both tubulin binding ability and cytotoxicity. The action of tubulin binding molecules induces cell cycle arrest in the G2-M phase, forming abnormal mitotic spindles and finally leading to apoptotic cell death. SB01 has initiated phase II clinical trial in head and neck squamous cell carcinoma (HNSCC). For more information, visit www.syncorebio.com.

Fresenius Kabi USA Acquires U.S. Pharmaceutical Plant and Ready-to-Administer Drugs from BD

Business Wire: January 8, 2016 – FRANKLIN LAKES, NJ, and LAKE ZURICH, IL, U.S.A. – Becton, Dickinson and Company (BD) (NYSE: BDX) and Fresenius Kabi USA announced today that Fresenius Kabi has acquired the BD Rx business, which includes a pharmaceutical manufacturing plant in Wilson, North Carolina, and the BD Simplist™ line of seven drugs in ready-to-administer prefilled glass syringes.

Fresenius Kabi and BD have also signed a 10-year supply and distribution agreement under which Fresenius Kabi will supply BD with a portfolio of intravenous solutions. Both BD and Fresenius Kabi plan to offer a range of IV solutions in the United States beginning in 2016.

Prefilled injectable medicines are designed to help improve patient care and safety by decreasing the number of steps in the traditional vial and syringe injection sequence, reducing the potential risk of medication error.

“Ready-to-administer, prefilled syringes are a growing segment in health care due to increased focus on medication safety and labor-saving efficiency,” said John Ducker, president and CEO of Fresenius Kabi USA. “They are a natural complement to our portfolio, enabling us to offer customers more choices and a broader range of specialty injectable medicines in vials as well as ready-to-administer presentations.”

The North Carolina plant, which employs about 100 people, features advanced pharmaceutical manufacturing and packaging technologies and was approved by the FDA in 2012. It currently produces seven drugs in ready-to-administer prefilled syringes and has capacity for future growth. Fresenius Kabi expects to invest in the facility over time, making it a global center of excellence for prefilled syringe production, the company said. The two companies will work together to assure a smooth transition for employees and customers.

“We believe Fresenius Kabi is a better owner for the BD Rx business, because it complements their existing capabilities in the injectable pharmaceutical industry,” said Tom Polen, president of BD’s medical segment. “In addition, we look forward to working with Fresenius Kabi to extend our medication management strategy through the addition of a portfolio of IV fluids, which will broaden our clinical and economical end-to-end solutions for our customers and their patients.”

Rani Therapeutics Announces Collaboration with MedImmune in the Metabolic Disease Field

PRNewswire: January 6, 2016 – SAN JOSE, CA, U.S.A. – Rani Therapeutics announced today that it has entered into a collaboration with MedImmune, the global biologics research and development arm of AstraZeneca, to evaluate Rani’s novel oral drug delivery platform. The companies have agreed to conduct feasibility studies over the next two years, in which Rani will test select biologic molecules in the area of metabolic disease to evaluate the oral delivery of these molecules.

Upon successful completion of the feasibility studies, AstraZeneca and MedImmune will have the right to enter into a more extensive collaboration with Rani.

Founded in 2012 and spun out of InCube Labs, Rani is developing a technology platform to convert injectable drugs such as TNF-alpha inhibitors, interleukin antibodies, basal insulin, and GLP-1 among others into oral pills. The company has demonstrated bioavailability similar to subcutaneous injections in early preclinical studies and has recently begun developing partnerships with pharmaceutical companies to test its platform with selected drugs.

“MedImmune has a growing portfolio of innovative biologics in the area of cardiovascular/metabolic disease, which is an important therapeutic area for AstraZeneca and MedImmune,” said Gail Wasserman, senior vice president, biopharmaceutical development, MedImmune. “Success in this program coupled with Rani’s technology could represent an innovative solution for delivering biologics orally to metabolic disease patients.”

“Our mission is to deliver biologics orally which would increase compliance and improve the lives of millions of patients worldwide,” said Mir Imran, chairman and CEO, Rani Therapeutics. “Our partnership with AstraZeneca and MedImmune marks our second collaboration with a multinational pharmaceutical company over the last year. These partnerships are major milestones for Rani and represent great validation of the potential of our technology.”

Rani announced a collaboration with Novartis in May 2015. Investors in Rani Therapeutics include Novartis, Google Ventures, InCube Ventures, and VentureHealth.

Rani Therapeutics has developed a novel approach for the oral delivery of peptides, proteins, and therapeutic antibodies that to date can only be delivered through injections. The approach and technology for Rani Therapeutics were developed at InCube Labs, a multi-disciplinary life sciences R&D lab focused on developing breakthrough medical innovations. InCube is led by Mir Imran, a prolific medical inventor, entrepreneur, and investor, who has founded more than 20 life sciences companies and holds more than 400 patents. Many of Imran’s innovations have resulted in new standards of care, including the first FDA-approved automatic implantable cardioverter defibrillator. For more information, please visit www.ranitherapeutics.com and www.incubelabs.com.

Clearside Biomedical, Inc., Announces Positive Topline Data from Phase 2 Clinical Trial for the Treatment of Macular Edema Associated with Noninfectious Uveitis

Business Wire: January 5, 2016 – ALPHARETTA, GA, U.S.A. – Clearside Biomedical, Inc., a late-stage clinical biopharmaceutical company developing innovative first-in-class drug therapies to treat blinding diseases of the eye, today announced positive results from the company's phase 2 clinical trial of CLS-TA, Clearside's proprietary form of triamcinolone acetonide, using suprachoroidal space (SCS™) drug administration for the treatment of macular edema associated with noninfectious uveitis.

The trial, referred to as the Dogwood trial, evaluated the safety and efficacy of CLS-TA in 22 patients with macular edema associated with noninfectious uveitis. In the trial, administration of CLS-TA resulted in a statistically significant mean change from baseline in central subfield thickness at eight weeks after one single treatment, which was the primary endpoint ($p = 0.0018$). Statistical significance was also achieved in the mean increase from baseline in best-corrected visual acuity ($p = 0.0004$), a secondary endpoint. There were no treatment-related serious adverse events reported in the trial, including no reported steroid-related increases in intraocular pressure (IOP), which is common in intravitreal and periocular drug delivery of corticosteroids. Clearside plans on submitting the full data set for presentation at an upcoming medical meeting.

"The data from this clinical trial continue to provide support for the approach to treatment of certain blinding eye diseases through SCS™ administration and the potential for an effective and safe option for the treatment of uveitis using CLS-TA, Clearside's proprietary triamcinolone acetonide formulation," said Daniel H. White, CEO and president of Clearside.

The Dogwood trial was the first masked, randomized clinical trial conducted in which drug was administered through the SCS™. This U.S., multi-center trial randomly assigned patients in a 4:1 ratio to receive a single injection of CLS-TA, 4 mg/100 µL or CLS-TA, 0.8 mg/100 µL. Subjects were treated at day 1 and were monitored for safety and efficacy for eight weeks following their SCS™ injection.

Clearside Biomedical has a portfolio of clinical and preclinical programs using drug administration through the SCS™ to provide a route of access to treat diseases of the back-of-the-eye like uveitis, retinal vein occlusion (RVO), wet age-related macular degeneration (AMD), and diabetic macular edema (DME). Clearside has enrolled its first patients in a phase 3 clinical trial (Peachtree) for the treatment of patients with macular edema associated with noninfectious uveitis; completed enrollment of a phase 2 clinical trial (Tanzanite) assessing the efficacy and safety of CLS-TA used concomitantly with an intravitreal injection of a VEGF inhibitor in patients with macular edema associated with RVO; and initiated IND-enabling studies for the treatment of AMD.

Clearside Biomedical, Inc., headquartered in Alpharetta, Georgia, is a late-stage clinical biopharmaceutical company developing innovative first-in-class drug therapies to treat blinding diseases of the eye using Clearside's proprietary SCS™ microinjector to reach diseased tissue through the SCS™. Clearside holds intellectual property protecting the delivery of drugs of any type through the SCS™ to reach the back of the eye. Visit www.clearsidebio.com for more information.

Rhythm and Camurus Announce License Agreement for Extended Release FluidCrystal Setmelanotide

Business Wire: January 5, 2016 – BOSTON, MA, U.S.A. and LUND, Sweden – Rhythm and Camurus (STO: CAMX) announced today a license agreement for the use of Camurus' drug delivery technology, FluidCrystal®, to formulate setmelanotide (RM-493), Rhythm's novel melanocortin-4 receptor (MC4R) agonist. Under the terms of the agreement, Camurus has granted Rhythm a worldwide license to the FluidCrystal technology to formulate setmelanotide and to develop, manufacture, and commercialize this new formulation that has the potential for once-weekly dosing, administered as a subcutaneous injection. Rhythm plans to initiate a phase I clinical trial with the setmelanotide FluidCrystal formulation after completing GMP manufacturing.

"We have developed a setmelanotide formulation with Camurus with an impressive sustained-duration profile," said Bart Henderson, president of Rhythm. "We believe this new formulation will provide a significant benefit to patients, improving compliance and ease of use with once-weekly dosing."

"The partnership with Rhythm follows the formulation development and preclinical assessment of this compelling drug candidate based on our FluidCrystal injection depot technology," said Fredrik Tiberg, president and CEO of Camurus. "Rhythm's setmelanotide represents a novel approach to treating patients suffering from life-threatening obesity due to these rare and serious genetic disorders."

The license granted to Rhythm is specific to the FluidCrystal technology incorporating setmelanotide. The formulation has been developed in a collaboration between the companies. Under the terms of the license agreement, Rhythm is responsible for manufacturing, development, and commercialization of the setmelanotide FluidCrystal formulation worldwide. Camurus is eligible to

receive an upfront payment and progressive payments of approximately \$65 million, of which the majority are sales milestones. In addition, Camurus is eligible to receive tiered, mid to mid-high, single digit royalties on future sales of the product.

Setmelanotide is a potent, first-in-class MC4R agonist in development for the treatment of obesity caused by genetic deficiencies in the MC4 pathway, a key pathway in humans that regulates energy expenditure, homeostasis, and appetite. The critical role of the MC4 pathway in weight regulation was validated with the discovery that single genetic defects along this pathway result in early onset and severe obesity. A phase 2 setmelanotide trial is ongoing for the treatment of Prader–Willi syndrome (PWS), a rare genetic disorder that causes life-threatening obesity. Recent scientific evidence implicates defects in the MC4 pathway as the likely cause of the weight and appetite abnormalities in PWS. A second phase 2 trial is ongoing for the treatment of pro-opiomelanocortin (POMC) deficiency obesity, a very rare, life-threatening genetic disorder of the MC4 pathway associated with unrelenting appetite and obesity.

The FluidCrystal injection depot delivers therapeutic levels of drug substance over extended periods—tunable from days to months—from a single injection. While traditional depot therapeutics comprise complicated microsphere technology, Camurus' depot offers a liquid solution that transforms into a controlled release liquid crystal gel matrix *in situ* on contact with minute quantities of aqueous fluid at site of injection. The FluidCrystal delivery system overcomes traditional side effects associated with high initial drug release on injection (drug burst) and poor drug stability by effectively encapsulating the drug compound in the nanopores of the depot matrix throughout the entire process from injection until final degradation. This, together with the ready-to-use product design, makes the system highly suitable for sustained parenteral delivery of peptides and proteins. FluidCrystal is a registered trademark of Camurus AB.

Immune Pharmaceuticals Announces New Data with Topical Cyclosporine Nano-Capsules in Dermatology

PRNewswire: January 4, 2016 – NEW YORK, NY, U.S.A. – Immune Pharmaceuticals Inc. (NASDAQ: IMNP), “Immune,” a clinical-stage biopharmaceutical company, announced today that following the review of new efficacy data, it has entered into an exclusive worldwide licensing and development agreement with BioNanoSim Ltd. (“BioNanoSim”), an Israeli nanotechnology drug delivery company, for a novel topical nano-capsule formulation of cyclosporine (also known as “cyclosporine-A” or “CsA”).

Monica Luchi, M.D., chief medical officer of Immune, commented: “Oral cyclosporine, a potent immunosuppressive drug, known to reduce the activity of the immune system by interfering with T-cells, has revolutionized transplantation medicine. Its use in dermatology has been limited to severe cases of psoriasis and atopic dermatitis, because of significant systemic toxicity. In a validated human skin model of atopic dermatitis, a novel topical nano-capsule formulation of cyclosporine A demonstrated comparable efficacy to a high potency topical corticosteroid. We believe that this product candidate could provide an important therapeutic alternative for millions of patients with chronic inflammatory skin disorders such as moderate atopic dermatitis and psoriasis. We intend to accelerate the development of this product candidate under the abbreviated 505(b)(2) drug development pathway permitted by the U.S. Food and Drug Administration.”

This topical nano-capsule formulation of cyclosporine incorporates a patented technology invented by professor Simon Benita, the former director of the Institute for Drug Research and head of the School of Pharmacy at the Hebrew University of Jerusalem. Prof. Benita has pioneered a nano-drug delivery platform for improving the absorption of poorly absorbed drugs. He recently succeeded in incorporating cyclosporine into a nano-capsule formulation that can be absorbed through the skin. In validated preclinical animal and human skin models, this new topical formulation was shown to deliver therapeutic levels of cyclosporine to targeted skin layers and to limit systemic absorption. “We believe that this collaboration with Immune will leverage our nanotechnology expertise and advance this novel product candidate into the clinic,” said Prof. Benita.

“This product candidate—topical cyclosporine nano-capsules—builds on Immune’s focused immuno-dermatology franchise. Bertilimumab, our clinical stage monoclonal antibody, is currently in phase II for the treatment of bullous pemphigoid, an orphan auto-immune skin disorder, and will be further developed for severe atopic dermatitis,” said Dr. Daniel Teper, Immune’s CEO.

Under terms of the agreement, Immune will fund further development of the product candidate, and BioNanoSim will be eligible to potentially receive certain development and regulatory milestones as well as royalties on sales. BioNanoSim is a nanotechnology drug delivery company formed by Prof. Simon Benita and Yissum, the technology transfer company of the Hebrew University of Jerusalem. Immune previously signed a memorandum of understanding with Yissum regarding the application of the technology.

Immune Pharmaceuticals (NASDAQ: IMNP) applies a personalized approach to treating and developing novel, highly targeted antibody therapeutics to improve the lives of patients with inflammatory diseases and cancer. Immune’s lead product candidate, bertilimumab, is in phase II clinical development for moderate-to-severe ulcerative colitis as well as for bullous pemphigoid, an orphan

auto-immune dermatological condition. Other indications being considered for development include atopic dermatitis, Crohn's disease, severe asthma, and NASH (an inflammatory liver disease). Immune recently expanded its portfolio in immuno-dermatology with topical nano-formulated cyclosporine-A for the treatment of psoriasis and atopic dermatitis. Immune's oncology pipeline includes bispecific antibodies, nanotherapeutics, including NanomAbs®, and several mid-to-late stage small molecules. Immune's non-core pipeline includes AmiKet™, a late clinical stage drug candidate for the treatment of neuropathic pain. For more information, visit Immune's website at www.immunepharmaceuticals.com, the content of which is not a part of this press release.

December

Braeburn Pharmaceuticals and Camurus Enroll First Patient in a Phase 3 Efficacy Trial of Long-Acting Treatment for Opioid Dependence

Business Wire: December 30, 2015 – PRINCETON, NJ, U.S.A. and LUND, Sweden – Braeburn Pharmaceuticals and Camurus (STO: CAMX) announce that the first patient has been randomized in the double blind phase 3 efficacy trial of CAM2038 in opioid-dependent patients. CAM2038 medications are designed for long-acting weekly and monthly administration. This randomized, double blind, active-controlled phase 3 trial is part of the registration program for CAM2038, which also includes two additional trials that were recently started, a phase 2 opioid blockade study and a long-term safety trial.

“We know through evidence-based research that long-term outpatient use of buprenorphine is essential in the treatment of opioid dependence. CAM2038 represents a novel approach, allowing personalized treatment with the potential to eliminate many of the challenges associated with current buprenorphine medications and take this treatment to a new level,” said Behshad Sheldon, president and CEO of Braeburn Pharmaceuticals. “With all three pivotal registration studies of CAM2038 for opioid dependence moving forward, we're now closer to delivering results that could have a real impact on the lives of people with opioid addiction and their families.”

Over the past decade, opioid addiction has become an epidemic in the United States, yet it is under-recognized and few medicines are in development for its treatment. A chronic, relapsing disease, opioid addiction can lead to overdose and death. The Center for Disease Control and Prevention (CDC) recently reported that opioid-related overdose deaths hit a record high in the United States of almost 29,000 in 2014, corresponding to nearly 80 deaths each day.

“The success of this trial has the potential to bring a paradigm shift in the way people with opioid dependence are treated,” said Dr. Rishi Kakar, Segal Institute, Florida. “CAM2038 will give physicians the ability to specialize treatment based on patients' needs and goals by providing both monthly and weekly dosing options.”

“This pivotal phase 3 study will provide essential insights about the use and potential of our long-acting CAM2038 medications in helping opioid-dependent patients to manage their disease more effectively,” said Fredrik Tibergh, president and CEO of Camurus. “We see a great deal of interest in the CAM2038 development program globally, from both patients and health care providers, and look forward to an expeditious enrollment and completion of the study during the second half of 2016.”

Braeburn Pharmaceuticals, an Apple Tree Partners company, is a pill-free pharmaceutical company delivering precision medicine in neuroscience. In September 2015 the Food and Drug Administration (FDA) accepted for review Braeburn's New Drug Application for its lead candidate, Probuphine®, a six-month buprenorphine implant for treatment of opioid addiction. The agency set February 27, 2016, as the target date for action. Long-acting therapeutic treatment options can be essential to improving patient outcomes and facilitating recovery in these conditions, which are often complicated by stigma and present significant public health challenges. Braeburn's investigational product pipeline consists of long-acting implantable and injectable therapies for serious neurological and psychiatric disorders, including opioid addiction, pain, and schizophrenia. Candidates include Probuphine®, a six-month buprenorphine implant for treatment of opioid addiction; CAM2038, weekly and monthly subcutaneous injection depot formulations of buprenorphine for treatment of opioid addiction and pain; a risperidone six-month implant for treatment of schizophrenia; and a novel molecule, ATI-9242, for treatment of schizophrenia. More information on Braeburn can be found at <http://braeburnpharmaceuticals.com>.

Oramed Announces Closing of Licensing and Investment Deal with HTIT for Oral Insulin Capsule in China

PRNewswire: December 29, 2015 – JERUSALEM, Israel – Oramed Pharmaceuticals Inc. (NASDAQ: ORMP) (www.oramed.com), a developer of oral drug delivery systems, today announced the closing of its previously announced license and investment deal with Hefei Tianhui Incubation of Technologies Co. Ltd. (“HTIT”). Oramed has sold 1,155,367 restricted shares of common stock at a price of \$10.39 per Share, for an aggregate amount of \$12 million. Oramed has additionally received approval from the Office of the Chief Scientist of the Israeli Ministry of Economy (“OCS”) for the out-licensing agreement with HTIT. Following receipt of the

OCS's approval, the out-licensing deal for ORMD-0801, a novel oral insulin capsule, has now closed. Under the terms of the agreement, Oramed has granted HTIT exclusive rights for commercialization of ORMD-0801 in greater China. The license includes multiple milestone payments aggregating \$38 million and up to a 10% royalty, based on net sales of the product in China.

"We are excited to have HTIT as a strategic partner as we enter into the huge and highly lucrative diabetes market in China," stated Oramed's CEO, Nadav Kidron. "We regard the closing of these transactions as a huge achievement and we now look forward toward our continued collaboration with the creative and experienced team at HTIT."

Oramed Pharmaceuticals is a technology pioneer in the field of oral delivery solutions for drugs currently delivered via injection. Established in 2006, Oramed's protein oral delivery (POD™) technology is based on over 30 years of research by top scientists at Jerusalem's Hadassah Medical Center. Oramed is seeking to revolutionize the treatment of diabetes through its proprietary flagship product, an orally ingestible insulin capsule (ORMD-0801). Having completed multiple phase IIa clinical trials, the company has started its phase IIb on type 2 diabetes under an Investigational New Drug application with the U.S. Food and Drug Administration. In addition, the company is developing an oral GLP-1 analog capsule (ORMD-0901).

NovaTears® Significantly Stabilizes the Tear Film and Relieves Dry Eye Symptoms in Patients with Evaporative Dry Eye Disease

Business Wire: December 16, 2015 – HEIDELBERG, Germany – NovaTears®, the first commercially available topical eye drop from Novaliq GmbH for the treatment of evaporative dry eye disease (DED), was found to significantly improve four of five measures associated with evaporative DED, new research shows. NovaTears was also shown to be safe and well tolerated, and caused no changes in visual acuity or intraocular pressure (IOP). The decrease of the ocular surface disease index (OSDI) by a mean of 21 points exceeded minimal, clinically important differences for mild or moderate and severe disease. These findings were published recently in the *Journal of Ocular Pharmacology and Therapeutics*.

Thirty patients with evaporative DED received NovaTears (perfluorohexyloctane F6H8) during a prospective, multicenter, observational, 6-week study. Subjects applied one drop of NovaTears to both eyes four times daily and returned six weeks later for followup. Parameters assessed included best-corrected visual acuity (BCVA), IOP, Schirmer I test, tear fluid, tear film breakup time (TFBUT), corneal staining, meibum secretion, and OSDI. Twenty-five subjects completed the study per protocol, of which 24 were female and one was male.

After six weeks of use, NovaTears treatment led to a significant reduction of corneal staining and a significant increase of Schirmer I and TFBUT. In addition, OSDI score dropped significantly from a mean of 55 (± 23.0) to 34 (± 22.4). Visual acuity and IOP did not change.

"These findings strongly suggest that NovaTears significantly and safely relieves many of the symptoms associated with evaporative DED," said study co-author Philipp Steven, M.D., principal investigator, Department of Ophthalmology, Ocular GvHD Competence Center, University of Cologne, Germany. "The decrease of the OSDI by a mean of 21 points is particularly remarkable and clearly exceeds minimal, clinically important differences for mild, moderate, and even severe disease. What's more, NovaTears' novel non-blurring, water-free formulation demonstrates strong spreading abilities due to an extremely low surface tension of just 19.65 mNm compared to water at 72 mNm."

The significant decrease in corneal staining can be seen in the shift of the number of patients diagnosed with grade 1 or grade 2 at baseline toward grade 0 at follow up. At baseline, 11 eyes were grade 0, 29 were grade 1, and eight were grade 2. At the end of the study, 37 eyes were grade 0, 10 were grade 1, and one eye was grade 2.

Tear secretion and tear film stability improved significantly over the study period, as can be seen in the increase in Schirmer I and the TFBUT. Schirmer I test showed increases from 10.5 ± 4.1 mm/5 min in the right eye to 16.6 ± 9.8 mm/5 min (OD: $p = 0.0040$), and in the left eye from 10.2 ± 4.2 mm/5 min to 15.9 ± 9.7 mm/5 min (OS: $p = 0.0013$). TFBUT increased from 6.0 ± 2.5 s in the right eye to 8.8 ± 4.9 s (OD: $p = 0.0026$), and in the left eye from 5.8 ± 2.6 s to 9.6 ± 5.9 s (OS: $p = 0.0006$).

Patient meibum was examined at both baseline and follow-up visit and improved in some cases. In seven cases, no expressible meibum was reported at study conclusion. Overall safety and tolerability was good, five adverse events were reported in the whole study, which were all of mild to moderate intensity.

"This new study supports the safety and efficacy of NovaTears and provides clinical endorsement for patients with evaporative dry eye disease," said Bernhard Günther, managing director and CEO of Novaliq GmbH.

“Novaliq’s study clearly demonstrates that NovaTears offers significant benefits to patients with evaporative dry eye disease and further validates Novaliq as an emerging company providing innovative ocular disease therapeutics,” said Jerry Cagle, Ph.D., board member, Novaliq GmbH. This study was supported by Novaliq GmbH, Heidelberg, Germany.

Novaliq GmbH, founded in 2007, is a Heidelberg based specialty pharmaceutical and drug delivery company with the mission to transform poorly soluble drugs into effective ocular therapeutics for both front and back of the eye. Novaliq’s proprietary 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®, with CE marking based on Novaliq’s proprietary EyeSol® technology. NovaTears is marketed under the brand name EvoTears™ in Europe. More on www.novaliq.com.

Nostrum Announcement of Its Acquisition of Sun’s Bryan, Ohio, Facility Along with Related Products and Employees

PRNewswire: December 15, 2015 – SOMERSET, NJ, U.S.A. – Nostrum Laboratories Inc. (“Nostrum”), a wholly owned subsidiary of Nostrum Pharmaceuticals, LLC, and a fully integrated specialty pharmaceutical company principally engaged in the development and commercialization of highly specialized, difficult to formulate, controlled release generic and branded drugs, announced today that it has acquired certain assets from a wholly owned subsidiary of Sun Pharmaceutical Industries Ltd. (“Sun Pharma”), including its liquids and semi-solids manufacturing facility in Bryan, Ohio, related products, and the unit’s employees. Nostrum also acquired additional products from Sun Pharma’s wholly owned subsidiaries, which products will be manufactured for Nostrum under separate agreement. Sun Pharma will transition all sales and marketing responsibilities for the aforementioned products to Nostrum. Terms of the transaction were not disclosed.

In connection with the transaction, Nostrum purchased the facility in Bryan, where Nostrum will manufacture the related products that it acquired from Sun Pharma and plans to develop and commercialize products there in conjunction with its manufacturing facilities in Kansas City, Missouri, and its affiliate’s research and development center in Mumbai, India.

Commenting on the asset purchase, Nostrum chairman and CEO Nirmal Mulye, Ph.D., said, “We are pleased to complete this transaction with Sun Pharma and believe this acquisition strengthens our revenue base and ensures that we fulfill our organic growth initiatives.”

Sun Pharma’s CEO for North America, Kal Sundaram, added, “This transaction is a winning proposition for all parties, as Nostrum Labs will continue to grow the Bryan facility through the introduction of new products, thus ensuring the continued employment of the employees at Bryan. Further, Sun Pharma will benefit from the collaboration with Nostrum Labs on product development opportunities in the future.”

Nostrum and its parent are engaged in the formulation and commercialization of specialty pharmaceutical products and controlled-release, orally administered, branded and generic drugs. Pharmaceutical companies are increasingly utilizing controlled-release drug delivery technologies to improve therapy. These technologies allow for the development of “patient-friendly” dosage forms, which reduce frequency of drug administration, thus improving patient compliance. Controlled-release pharmaceuticals can be especially beneficial for certain patient populations, such as the elderly, who often require several medications with differing dosing regimens. Nostrum has a rich portfolio of filed intellectual property. Nostrum’s rich portfolio is supported by research and development in India through its affiliate, Enem Nostrum Remedies Pvt. Ltd.

Transdermal Delivery Solutions Announces Commencement of Clinical Trials of Hormone Replacement Technologies’ Testagen® HypoSpray®

Business Wire: December 7, 2015 – PALM BEACH GARDENS, FL, U.S.A. – Transdermal Delivery Solutions Corporation (TDSC), www.TDSC.us, announced today entering a pivotal phase of clinical trials. The British National Health Service (NHS) Ethics filings (IRAS) preliminary to the Medicine and Health Products Review Authority’s (MHRA) approval of clinical trial applications (CTA) for TDSC’s investigational medical product dossier on hormone replacement technologies’ Testagen® HypoSpray® were filed on November 25 and 30, 2015. NHS Ethics will review the protocols together on December 16, 2015.

“We are pleased to reach this milestone and expect our progress with the technology to accelerate rapidly from here,” said Kenneth Kirby, president of TDSC. “As with any drug delivery FDA-approval process, it’s been a long road of regulatory channels over the course of its development. It’s exciting to begin this final stage of testing with TDSC.”

Prof. Shern Chew and faculty from Barts and the London NHS at a partner facility, the Advanced Therapies Centre of the London Clinic, will perform the clinical trials. Scientific advisors Profs. Richard Langford, Arthur Tucker, Atholl Johnston, and Howard Maibach of UC San Francisco will oversee the research.

These initial studies in patients will establish the ideal initial dose range for following studies and validate earlier research that established HypoSpray technology's greatly reduced potential for inadvertent transference to others. The CTAs are expected to be approved in 60 days or less, and patient screening will begin immediately upon MHRA's approval of the CTAs. These studies should be completed over the next 3-month period.

Testagen® TDS has been under evaluation for over 10 years and is designed to address the safety problems associated with transdermal and oral hormone replacement therapies. The FDA has released the product for trials both here and in the United Kingdom. The patented treatment formulation is expected to revolutionize testosterone replacement as the system provides faster absorption while avoiding liver interactions and dramatically lowers transferable concentrations left on the skin. www.tdsc.us/lower.php?url=testagen

Cipla Launches Novel "5 in 1" Anti-aging Skin Care Product Cutisera™ Developed by Stempeutics

PRNewswire: December 4, 2015 – BANGALORE, India – Cipla Ltd., a global pharmaceutical company, announced today that it has launched a novel "5 in 1" anti-aging skin care product, Cutisera™, developed by Stempeutics. Cutisera™ has been developed using bioactive factors derived from human adult stem cells to enhance the rejuvenation of aging skin. The active ingredients have been tested for *in vitro* and *in vivo* efficacy. The product has been dermatologically tested with human volunteers with features of aging skin over a period of 3 months, wherein the product was applied twice a day. This human study has demonstrated Cutisera's effectiveness as a powerful and yet soothing anti-aging skin care product suitable for all skin types of Indian origin. The formulated product does not contain any stem cells.

Commenting on the Cutisera launch, Mr. Chandru Chawla, head of Cipla New Ventures, said, "We are excited to launch Cutisera™—the next generation bioengineered skin care product. As we age and get exposed to environmental stressors, the production of human growth factors within skin is depleted, giving rise to features of aging skin. By reintroducing these factors through daily application of Cutisera, damaged skin cells are repaired, resulting in rejuvenation of the skin."

"We are pleased to market Cutisera™ through our JV partner Cipla," said Mr. BN Manohar, CEO of Stempeutics. "Already physician and consumer interest in Cutisera™ has been high. Cutisera™ has been developed using a unique and proprietary patent-pending technology that produces stable key ingredients containing growth factors and cytokines in specified amounts—batch after batch. This results in a consistent high quality product benchmarked globally."

Dr. Jaideep Gogtay, chief medical officer of Cipla, said, "Improved technology and increased awareness are making people more concerned about their skin. This is driving them to look for skincare products that will not only slowdown the aging process but will also maintain their youthful look for a longer period. It is important to first understand what causes aging and then dealing with the underlying causes. Cutisera™ exactly does the same. It assists the body's natural biological repair processes to treat damaged skin and prevent further damage."

Cipla is a global pharmaceutical company that uses cutting-edge technology and innovation to meet the everyday needs of all patients. For 80 years, Cipla has emerged as one of the most respected pharmaceutical names in India as well as across more than 150 countries. Our portfolio includes 1,500-plus products across therapeutic categories with one quality standard globally. While delivering a long-term sustainable business, Cipla recognises its duty to provide affordable medicines. Cipla's emphasis on access for patients was recognized globally for the pioneering role played in HIV/AIDS treatment as the first pharmaceutical company to provide a triple combination anti-retroviral (ARV) in Africa at less than one dollar a day and thereby treating many millions of patients since 2001. Cipla's research and development focuses on developing innovative products and drug delivery systems.

Stempeutics is an advanced clinical stage biotech company based out of Bangalore. It was founded by Manipal Education and Medical Group (MEMG) in 2006 and later entered into a strategic alliance with Cipla in 2009. Stempeutics' strength lies in developing innovative stem cell products by nurturing cutting-edge research and clinical applications through dedicated efforts of its highly qualified team. Its goal is to develop novel stem cell drugs addressing major unmet medical needs with an India first, global next approach.

Acorda Initiates Phase 1 Clinical Trial of CVT-427, Inhaled Therapy for Acute Treatment of Migraines

Business Wire: December 3, 2015 – ARDSLEY, NY, U.S.A. – Acorda Therapeutics, Inc. (Nasdaq: ACOR) today announced initiation of enrollment in the first clinical study of CVT-427, an investigational agent under development for the acute treatment of migraines.

continued

“CVT-427 represents an innovative approach to acute treatment of migraines. Applying Acorda’s proprietary ARCUS technology, we have developed an inhaled version of a well-established migraine therapy,” said Sean Plunkett, executive director, device and program management at Acorda. “We are excited about evaluating the potential of CVT-427 to offer a unique way to treat people with migraine who are not completely satisfied with their current options.”

CVT-427 is a novel, inhaled formulation of zolmitriptan that uses the company’s proprietary ARCUS® technology. Zolmitriptan belongs to a class of drugs known as triptans, which are a leading therapy for acute treatment of migraines. Triptans are most commonly administered orally, usually as a pill.

Oral migraine therapies can be associated with slow onset of action, as the medicine is absorbed through the gastrointestinal (digestive) tract before reaching the brain. Another consideration in acute treatment of migraine is nausea. It is estimated that almost 90% of people living with migraines have experienced nausea at least once during a migraine attack. Nausea and vomiting can be so debilitating that people either delay or completely forgo taking an oral medication; more than 50% of migraine sufferers experience this degree of nausea with the majority of their migraine attacks. Inhaled treatments, such as those that utilize the ARCUS technology, enter the body rapidly through the lungs, bypassing the digestive system.

Acorda’s proprietary ARCUS technology platform is a dry-powder pulmonary delivery system that has potential applications in multiple disease areas. This platform allows consistent and precise delivery of significantly larger doses of medication than are possible with conventional pulmonary systems. The ARCUS inhaler is breath-actuated, operated by the user putting their lips to the device and simply breathing in.

The ARCUS technology has been used to successfully deliver more than one million doses to patients in clinical trials of various products. There are currently two clinical stage programs using the ARCUS technology: CVT-301 (phase 3) is in development as a treatment for off episodes in Parkinson’s disease; CVT-427 (phase 1) is in development for the acute treatment of migraines. Acorda has an extensive patent portfolio relating to CVT-301, CVT-427, and the ARCUS technology, which covers aspects of the formulated drug product, the inhaler, the method of drug delivery, and manufacturing processes.

Founded in 1995, Acorda Therapeutics is a biotechnology company focused on developing therapies that restore function and improve the lives of people with neurological disorders. For more information, please visit the company’s website at www.acorda.com.

InVivo Therapeutics Announces Bioengineered Neural Trails™ Program for Chronic Spinal Cord Injury

Business Wire: December 2, 2015 – CAMBRIDGE, MA, U.S.A. – InVivo Therapeutics Holdings Corp. (NVIV) today announced an innovative strategy for the treatment of chronic spinal cord injury (SCI). The company will focus its research efforts for chronic SCI on Bioengineered Neural Trails™. Bioengineered Neural Trails are injectable combinations of biomaterials and neural stem cells (NSCs) delivered using minimally invasive surgical instrumentation and techniques to create trails across the chronic injury site. To support this strategy, InVivo has entered into agreements with the University of California, San Diego (UC San Diego) and James Guest, M.D., Ph.D., to expand the company’s intellectual property portfolio. InVivo entered into an exclusive license agreement with UC San Diego for issued U.S. patent 9,011,410 titled “Spinal Multisegmental Cell and Drug Delivery System,” and into an assignment agreement with Dr. Guest for issued U.S. patent 7,666,177 titled “Method and System for Cellular Transplantation in the Spinal Cord.” InVivo also has filed a provisional application in support of the Bioengineered Neural Trails program titled “Methods and Systems for Delivery of a Trail of a Therapeutic Substance.”

“Our goal is to restore neuronal connectivity and thereby promote neurological recovery in people with chronic SCI,” said Tom Ulich, M.D., chief scientific officer of InVivo. “Our minimally invasive therapeutic approach is to bridge the spinal cord lesion at the time of implantation with a trail of NSCs delivered in an injectable and biodegradable soft, gel-like scaffold. We look forward to presenting our preclinical results in the spinal cords of small and large animals during the key opinion leader event and company update on Thursday.”

Mark Perrin, chief executive officer and chairman of InVivo, said, “We are excited about our novel Bioengineered Neural Trails program for the treatment of chronic spinal cord injury. The newly secured patents along with our provisional patent application provide the intellectual property foundation for our Bioengineered Neural Trails program.” To learn more about our approach to chronic spinal cord injury, visit the InVivo Therapeutics website: www.invivotherapeutics.com/research-clinical-development/pipeline/bioengineered-neural-trails.

Bioengineered Neural Trails are injectable combinations of biomaterials and neural stem cells (NSCs) delivered using minimally invasive surgical instrumentation and techniques to create trails across the chronic spinal cord injury site. InVivo’s Bioengineered

Neural Trails program is currently being advanced preclinically by the research and development team at InVivo for the treatment of chronic spinal cord injury.

InVivo Therapeutics Holdings Corp. is a research and clinical-stage biomaterials and biotechnology company with a focus on treatment of spinal cord injuries. The company was founded in 2005 with proprietary technology co-invented by Robert Langer, Sc.D., professor at Massachusetts Institute of Technology, and Joseph P. Vacanti, M.D., who then was at Boston Children's Hospital and who now is affiliated with Massachusetts General Hospital. In 2011, the company earned the David S. Apple Award from the American Spinal Injury Association for its outstanding contribution to spinal cord injury medicine. In 2015, the company's investigational Neuro-Spinal Scaffold™ received the 2015 Becker's Healthcare Spine Device Award. The publicly traded company is headquartered in Cambridge, Massachusetts. For more details, visit www.invivotherapeutics.com.

PolyPid Announces First Patient Enrolled in Confirmatory Clinical Trial, Evaluating Performance and Safety of BonyPid-1000™, an Antibiotic Eluting Bone Void Filler

PRNewswire: December 2, 2015 – PETAH TIKVA, Israel – PolyPid Ltd., an emerging clinical stage specialty pharmaceutical company focused primarily on the development of postsurgical anti-infection pipeline, announced today the enrollment of the first patient in the confirmatory clinical trial of BonyPid-1000™, a doxycycline loaded synthetic bone substitute.

The BonyPid-1000-103 trial is a randomized, single-blind standard of care controlled study and is expected to be conducted on a total of 64 patients with severe open tibia fractures (Gustilo IIIA and IIIB) at five sites in Israel and three in Asia. The primary endpoint of the study is to determine performance and safety of BonyPid-1000™ on bone healing in traumatic open fracture patients, over a period of 6 and 12 months, compared with standard of care. The first patient has been enrolled at the Tel Aviv Sourasky Medical Center, Israel.

Dr. Noam Emanuel, PolyPid's CTO, stated "We are very pleased to commence our final, CE mark certification clinical trial for BonyPid-1000™, our PLEX based product addressing such a significant unmet medical need. This study expands our existing successful clinical data." Dr. Emanuel added, "Severe open fracture patients are highly prone to infection at the fracture site, causing an increased number of surgical interventions, longer healing time, and higher amputation rates."

BonyPid-1000™ is a bone graft substitute containing a broad-spectrum antibiotic, doxycycline hyclate, to reduce microbial colonization on the bone void filler. The antibiotic is released locally over a prolonged period of four weeks. BonyPid-1000™ has successfully completed pilot clinical trials in open fracture indication, demonstrating excellent safety and efficacy results, including 0% infections in the target fracture and 0% amputations after 6–12 months follow up (versus an average of 25 and 7%, respectively, in a historical control group of patients).

PolyPid is a clinical stage, emerging specialty pharmaceutical company developing, manufacturing, and commercializing products based on a proprietary platform named PLEX™ (Polymer-Lipid Encapsulation matriX), in the field of extended release, local drug delivery. PLEX™-based protected drug reservoirs enable prolonged delivery of drugs, including biologics, over periods ranging from days to several months. The application of PLEX™ technology enables optimized drug treatment regimens by predetermining release rates and durations, a rare combination of attributes.

PolyPid's lead product, D-PLEX™, is a secured antibiotic drug reservoir. It provides a safe and effective local anti-bacterial preventive measure and eradication at the target site by administration during surgical procedures. After surgery the reservoir constantly releases the entrapped antibiotic over several weeks. It thus allows for prolonged infection prevention or treatment and also has the potential to eradicate resistant bacteria. For additional company information, visit www.polypid.com.

Patent Granted for Additional Polymer Technology Originated at Particle Sciences

PRNewswire: December 1, 2015 – BETHLEHEM, PA, U.S.A. – Eyeon Therapeutics has received a Notice of Allowance for additional novel dry eye treatments based on a charged hydrophilic polymer developed at Particle Sciences, a leading drug delivery CDMO. The product has been shown to be safe and effective in a small trial previously published. CEO Mark Mitchnick, M.D., states, "This second set of claims broadens the protection to additional polymers in conjunction with a therapeutic agent. Nanoparticles coated with the novel polymers are also covered. We believe there is very substantial value to this approach and look forward to continuing to help Eyeon develop the technology."

David Kleinman, M.D., CEO of Eyeon Therapeutics, commented, "Dry eye is a serious and growing problem for which there are few effective therapies. Our product offers a unique approach that is clinically validated and useful in a number of ocular applications. In the coming months we will be pursuing partnerships and expanded protection around this product and follow-ons."

continued

November

Debiotech and ARTORG Initiate an Exclusive Collaboration on the Next Generation Artificial Pancreas

PRNewswire: November 24, 2015 – LAUSANNE and BERN, Switzerland – Debiotech SA, the ARTORG Center for Biomedical Engineering Research of the University of Bern, and the Division of Endocrinology, Diabetes and Clinical Nutrition of the Bern University Hospital (“Inselspital”) are proud to announce the start of an exclusive collaboration to develop a novel generation artificial pancreas. Combining a fully new control algorithm for the personalised delivery of insulin for diabetic patients with the unequalled accuracy of a MEMS based pump, the three partners’ ambition is to create a substantial change in the treatment of diabetes and in the market for the artificial pancreas.

The artificial pancreas is often presented as the holy grail of diabetes treatment. “Today, a diabetic patient must follow a very constraining therapy with many blood glucose measurements, dose calculations, and insulin injections. The ideal would be to have a single system that can conduct all of these operations without requiring any intervention,” said Peter Diem, M.D., professor and head of the Division of Endocrinology, Diabetes and Clinical Nutrition of the “Inselspital.” On the one hand, such systems require a continuous glucometer that every minute will measure and calculate the level of glucose present in the blood and, on the other hand, an infusion pump that will continuously deliver insulin. The amount of infused insulin is determined by an algorithm that estimates the patient needs based on the measured glucose levels, the time of day, or the expected activities and that will adapt the pump infusion rate accordingly. “Approaches taken so far do not resolve fundamental difficulties: the patients’ variability, uncertainties related to system disturbances (e.g., food intake and physical activity), and errors related to the used devices. The proposed algorithm is easy to use, introduces the concept of real-time personalisation based on reinforcement learning, a machine learning method, is able to tackle inter- and intra-patient variability, and can compensate for the effects of uncertain events,” said Stavroula Mougiakakou, Ph.D., head of the Diabetes Technology Research Group at the ARTORG Center.

The system will include the JewelPUMP developed by Debiotech, and the algorithm will run on the wireless PDA device used today for the programming of the pump. “Our objective has always been to bring innovation that can better serve patient needs and improve quality of life,” said Frédéric Neftel, president and CEO of Debiotech. “The JewelPUMP, with its unique accuracy and safety features, offers an ideal platform to develop new approaches for an artificial pancreas. ARTORG has been working for many years on new algorithms, outside the conventional approach, which could open new perspectives for a more intelligent artificial pancreas. We are delighted to enter into this partnership with both clinical experts and engineers in the heart of Switzerland.”

The JewelPUMP is a patch pump, directly placed on the skin, that can be detached and reattached at will. It is waterproof and includes several sensors to continuously monitor therapy. It has been used by patients in a clinical trial for several days at home, and its reception has been very enthusiastic. The accuracy of the different elements in an artificial pancreas is critical. The insulin levels have to be maintained in a very narrow window. Too little insulin will lead to hyperglycaemia, while too much insulin generates hypoglycaemia. Both situations may induce coma and even patient death. “The scrutiny on pump accuracy has increased in recent years. *In vitro* and *in vivo*, the JewelPUMP has shown its ability to inject the programmed dose very accurately. Combining the algorithm developed by ARTORG with Debiotech’s JewelPUMP has the potential to revolutionise the way we approach the artificial pancreas,” said Laurent-Dominique Piveteau, COO of Debiotech.

After development and integration, the algorithm will be tested in different clinical trials. “We are looking forward to seeing this new approach being used by patients and appreciate how much this may facilitate their treatment. It is even more important to improve their quality of life,” said Christoph Stettler, M.D., professor and newly elected director of the Division of Endocrinology, Diabetes and Clinical Nutrition at the “Inselspital.”

The Medicines Company Receives European Commission Approval for IONSYS® 40 Micrograms per Dose Transdermal System (Fentanyl) to Treat Postoperative Pain in Adult Hospitalized Patients

Business Wire: November 20, 2015 – PARSIPPANY, NJ, U.S.A. – The Medicines Company today announced that the European Commission has granted marketing authorization for IONSYS® (40 micrograms per dose transdermal system), with active ingredient fentanyl, for the management of acute moderate-to-severe postoperative pain in adult patients for use in the hospital. IONSYS will be the only needle-free, patient-controlled, preprogrammed iontophoretic transdermal delivery system for use in adult patients requiring opioid analgesia in EU hospital settings.

The marketing authorization follows the issuance of a positive opinion in September by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and is now valid in the 31 countries of the European Economic Area (EEA), which includes all 28 European Union (EU) member states, plus Norway, Iceland, and Liechtenstein.

"I welcome the return of IONSYS as an option for postoperative pain management, as it provides patient-activated, needle-free transdermal delivery of a strong pain relieving medicine," said Prof. Richard Langford, consultant in anaesthesia and pain medicine, Pain and Anaesthesia Research Centre, St. Bartholomew's Hospital, Barts Health NHS Trust, London. "This self-contained adhesive drug delivery system has been shown in trials to be easy to use and is not reliant on intravenous access. Both patients and staff gave IONSYS higher scores for postsurgery patient mobilisation and rehabilitation, as well as for overall patient and staff satisfaction."

Globally, hospitals perform 234 million major surgeries per year, and approximately 75% of patients experience pain postoperatively. Many of these patients continue to suffer from poorly managed pain days or weeks after their procedures. For example, a comprehensive assessment of 1,490 postsurgical patients in the Netherlands demonstrated that 15% reported moderate-to-severe pain four days after their surgeries. This is consistent with data from the United States that indicated 86% of inpatient surgeries result in pain up to two weeks following the procedure.

The trend toward patient-controlled medication delivery for postoperative pain has been accelerating in Europe, the United States, and other developed countries. The most comprehensive data available shows that in the United States alone, 1.4 million patients now manage their pain using intravenous patient-controlled analgesia (IV-PCA). Unlike traditional IV-PCA, IONSYS delivers on-demand fentanyl via an imperceptible electric current (iontophoresis) triggered by the simple double press of a button on a credit-card-sized device.

"The management of postoperative pain remains a growing challenge for the healthcare community, with many patients continuing to suffer from poorly managed pain long after their procedures," said Clive Meanwell, M.D., Ph.D., chief executive officer, The Medicines Company. "IONSYS offers a patient-controlled, needle-free system that delivers effective doses of a potent analgesic, fentanyl, allowing patients to be free of IV lines so they can be more mobile during recovery."

A supplemental new drug application for IONSYS was approved by the U.S. Food and Drug Administration (FDA) in April 2015 with an approved IONSYS Risk Evaluation Mitigation Strategy (REMS) program. The product is commercially available in the United States as of July 2015. For more information, visit www.themedicinescompany.com.

Orexo: New Abstral® Partner in the United States

Business Wire: November 20, 2015 – UPPSALA, Sweden – Orexo AB (publ) (STO: ORX) today announced that the U.S. Abstral partner, Galena Biopharma Inc., has divested its Abstral business to the privately held company Sentyln Therapeutics Inc. as a consequence of Galena's change of strategy to focus on its clinical development programs. The divestment is effective as of November 19, 2015, and Orexo terms are unchanged and passed on from Galena to Sentyln.

"We are pleased to see the interest in Abstral that has been revealed during Galena's divestment process and pleased to have a new and dedicated partner in Sentyln. We are confident that Sentyln will manage to continue to grow the Abstral business in the United States," said Nikolaj Sørensen, CEO and president of Orexo AB.

Abstral is the leading fast-acting fentanyl product in the EU intended for treatment of breakthrough pain in cancer patients. Abstral employs Orexo's proprietary sublingual delivery technology (under the tongue). After the product development Abstral was out-licensed to Kyowa Hakko Kirin Co., Ltd., and the European subsidiary ProStrakan Group plc, which still hold the rights in Japan and the EU, respectively, whereas Galena Biopharma Inc. held the rights for Abstral in the United States until the divestiture to Sentyln Therapeutics Inc. as of November 19, 2015. For information about Abstral, please visit www.abstral.com.

Celator® Pharmaceuticals Receives Allowance of Expanded U.S. Claims on CombiPlex® Technology

PRNewswire: November 19, 2015 – EWING, NJ, U.S.A. – Celator Pharmaceuticals, Inc. (Nasdaq: CPXX) today announced that it was given a notice of allowance of claims by the U.S. Patent and Trademark Office for the patent "Compositions for Delivery of Drug Combinations." This patent covers the company's proprietary CombiPlex technology, and the allowed claims increase the scope of drug delivery vehicles covered by the patent.

Celator recently announced the successful application of its proprietary CombiPlex technology to drug combinations incorporating molecularly targeted agents (MTAs), where marked improvements in pharmacokinetics, tolerability, efficacy and drug ratio-dependent efficacy were achieved. The chemical features of many MTAs require drug carriers capable of co-encapsulating hydrophobic drugs, and the allowed claims now broadly cover micelles, polymer nanoparticles, polymer microparticles, polymer-lipid hybrid systems and derivatized single chain polymers. These types of drug carriers are often used to encapsulate hydrophobic drugs for systemic delivery.

“This is an important development for our CombiPlex platform,” said Dr. Lawrence Mayer, president and chief scientific officer at Celator. “The repertoire of drug carriers now covered by the patent claims positions Celator for leadership in a space where evidence is mounting that improved delivery of MTA combinations could overcome significant challenges experienced with conventional formulations of these agents. We expect this will strengthen our ability to pursue R&D collaborations with biopharmaceutical companies.”

ForSight VISION5's Phase 2 Clinical Data Demonstrating Six-Month IOP-Lowering from a Single Topical Ocular Insert with Very High Retention Rates Presented at American Academy of Ophthalmology

PRNewswire: November 17, 2015 – MENLO PARK, CA, and LAS VEGAS, NV, U.S.A. – ForSight VISION5 announced results of its first randomized, controlled phase 2 study comparing the investigational Helios™ bimatoprost ocular insert to twice-daily timolol eye drops. The presented data demonstrated that a single administration of the investigational Helios™ bimatoprost ocular insert provided sustained reduction in intraocular pressure (IOP) for six months and IOP reduction of 4–6 mmHg at the study's primary endpoint of 12 weeks. Approximately 90% of subjects retained inserts in both eyes for 6 months without clinician assistance. The Helios™ preservative-free bimatoprost ocular insert is designed to provide sustained IOP-lowering for patients who cannot or do not take their prescribed eye drops. IOP lowering has been shown to reduce visual field loss in patients with ocular hypertension and open-angle glaucoma.

The phase 2 results comprise data from 130 subjects and were collected from 10 clinical sites in the United States in a randomized, double-masked, active-controlled trial of the bimatoprost ocular insert compared with twice-daily timolol eye drops. To achieve masking, subjects in the bimatoprost insert arm used concomitant unpreserved artificial tears, and subjects in the timolol eye drop arm used concomitant nonmedicated ocular inserts. The data were presented today by Prof. James D. Brandt, principal investigator of the study and director of the Glaucoma Service at the University of California Davis Health System, at the American Academy of Ophthalmology (AAO) annual meeting.

Highlights of the clinical results include:

- Mean diurnal IOP after washout was 23.8 mmHg. A sustained reduction in IOP from a single dose of the bimatoprost insert was observed to be 4–6 mmHg across the three diurnal time points at the primary endpoint of 3 months, and clinically relevant IOP reduction continued through 6 months.
- Over the six-month period, the single dose of the bimatoprost insert (OU) lowered IOP by an average of one less mmHg than the 360 drops of timolol applied to each eye in the other arm of the study. This amount of IOP lowering is considered to be clinically relevant since the product candidate is designed to address the needs of patients who are nonadherent to their eye drops.
- The primary efficacy endpoints consisted of comparisons of the bimatoprost insert arm to the timolol drops arm at each of three diurnal time points (T = 0, 2, and 8 hours) at each of weeks 2, 6, and 12 of treatment. Secondary endpoints consisted of the same diurnal time point comparisons at months 4, 5, and 6. While the confidence intervals in this limited study did not meet the test for statistical noninferiority to timolol, the results suggest that a larger-scale phase 3 study could achieve data that would be appropriate for registration with the FDA.
- Subjects found the inserts comfortable with approximately 90% of subjects experiencing acceptable comfort of a nonmedicated insert during the washout phase of the study.
- 88.5% of subjects retained the inserts in both eyes for 6 months without the aid of a clinician, and in all cases in which an insert was dislodged, the subject was aware of dislodgement.

There were no reported serious or unexpected ocular adverse events in the bimatoprost insert group. The most frequent treatment-emergent adverse events in the bimatoprost insert group (≥5% of subjects) were eye discharge (16%), conjunctival hyperemia (14%), punctate keratitis (13%), eye pruritis (11%), and ocular discomfort (6%) and were mostly transient.

“We know that a significant portion of our patients struggle with IOP-lowering eye drop adherence and persistence and that inadequate eye drop usage leads to vision loss,” said Brandt. “A well-tolerated, well-retained, topical sustained drug delivery system that provides clinically relevant IOP lowering for six months would allow us to treat these patients in a meaningful way.”

ForSight VISION5 continues to advance the clinical development of the Helios insert. The company recently also completed a phase 2 dose-ranging study (FSV5-004) that enrolled 121 subjects at 10 clinical sites in the United States in under nine weeks. The company intends to initiate a phase 3 clinical program in 2016.

“There is tremendous unmet need for a drug delivery mechanism that can deliver therapeutic levels of IOP lowering medication without requiring penetration of ocular tissue such as the sclera, cornea or conjunctiva in patients with glaucoma and ocular hypertension,” said Dr. Kuldev Singh, professor of ophthalmology and director of the Glaucoma Service at Stanford University School of Medicine. “In addition to addressing the enormous problem of poor adherence to glaucoma medications, a drug delivery approach that encourages patients to return every few months for treatment may also improve disease surveillance, allowing for appropriate adjustment of therapy,” added Singh, who cited recent work with collaborators from the University of California San Francisco that suggests that poor follow-up may be an independent risk factor for glaucoma progression.

The company is also pleased that the safety and retention data from the study presented today further validate the ForSight VISION5 ocular insert as a potential delivery system for other ophthalmic drugs to treat a variety of additional indications. For more information, please visit www.forsightvision5.com.

Zicam® Launches First-Ever Cold Remedy Nasal Swab with Plant-Based Ingredients – Just in Time for Cold Season

PRNewswire: November 12, 2015 – BRIDGEWATER, NJ, U.S.A. – Zicam®, a leading provider of over-the-counter homeopathic cold and allergy relief products, today announced the release of the completely reformulated Zicam® cold remedy nasal swabs, the only nasal swab clinically proven to shorten the duration of a cold when taken at the first sign. Due to consumer demand, Zicam® has brought back the convenient swab applicator that opens with a snap to deliver the new patented, plant-based formula.

“It’s time for people to stop thinking that there is nothing they can do when suffering from a cold,” said Dr. Holly Lucille, ND, RN, a renowned naturopathic doctor. “As we enter cold season, having safe and effective products, such as Zicam® cold remedy nasal swabs, is extremely beneficial in helping to get over a cold faster and get us back to our lives.”

The new Zicam® cold remedy nasal swabs have been clinically proven to shorten the duration of a cold when taken at the first sign. They also lessen the severity of common cold symptoms such as nasal congestion, watery eyes, runny nose, sneezing, and dry, scratchy throat. The unique formula is delivered in Zicam’s proprietary swab form, allowing for gentle application in nasal passages. The formula is homeopathic, zinc-free and provides cooling menthol and eucalyptus to help soothe upon application.

“At Zicam®, we’re dedicated to finding ways to help people feel better faster,” said M’lou Walker, CEO of Matrixx Initiatives, maker of Zicam. “Our new, clinically proven cold remedy nasal swabs were developed to help shorten colds so that users can step up and seize the day.”

Cerulean Announces Data at the 2015 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics

Business Wire: November 9, 2015 – CAMBRIDGE, MA, U.S.A. – Cerulean Pharma Inc. (NASDAQ: CERU), a clinical-stage company developing nanoparticle-drug conjugates (NDCs), today announced that data from an investigator-sponsored trial (IST) with its lead compound, CRLX101, in patients with advanced gastric cancers was presented at the 2015 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics on November 7. In this study, pre- and post-tumor treatment biopsies show the presence of CRLX101 and its anti-cancer payload in tumors and an almost exclusive absence of both from surrounding normal tissue. Importantly, inhibition of the molecular targets of CRLX101 was demonstrated in post-treatment biopsies. These data represent the first demonstration in humans that CRLX101 localizes in tumor tissue with corresponding expected molecular effects and that it spares surrounding healthy tissue.

“For the first time, we have clinical evidence that Cerulean’s Dynamic Tumor Targeting™ platform creates NDCs that preferentially target tumors, while sparing neighboring normal tissues,” stated Mark Davis, Ph.D., Warren and Katharine Schlinger Professor of Chemical Engineering at California Institute of Technology and a member of the City of Hope Comprehensive Cancer Center. “We have previously published tumor targeting of CRLX101 in animals, but we now have shown convincingly that this phenomenon is equally applicable in people.”

In addition, Cerulean presented preclinical posters at the meeting describing selective tumor localization of CRLX101 in mice and *in vitro* and *in vivo* studies demonstrating sustained drug release for multiple anti-cancer payloads and improved anti-cancer effects.

Acura Earns Accolades from Frost & Sullivan for Developing a Novel Technology Platform to Prevent the Abuse of Opioid-Based Medication Through Oral Administration

PRNewswire: November 9, 2015 – MOUNTAIN VIEW, CA, U.S.A. – Based on its recent analysis of the opioid oral abuse deterrence market, Frost & Sullivan recognizes Acura Pharmaceuticals, Inc. (Acura) (Nasdaq: ACUR), with the 2015 North American Frost &

Sullivan Award for Technology Innovation. Acura's development of the Limitx™ technology may go a long way in helping curb opioid abuse and prevent overdose and addiction. The company is supported by a grant from the National Institutes of Health (NIH) in developing this novel technology.

The Centers for Disease Control and Prevention terms drug abuse an epidemic, as it affects millions worldwide. Acura is combating this menace with Limitx™. Laboratory tests conducted by Acura have confirmed the ability of Limitx™ to restrict the immediate release of the active pharmaceutical ingredient (API) into simulated gastric fluid when multiple tablets are consumed at once, either intentionally or accidentally.

"Limitx™ supersedes existing formulations that are incorporated in immediate-release opioid prescription pain killers," said Frost & Sullivan research analyst Karan Verma. "The lack of other abuse-deterrent products in the market that focus on oral abuse makes the Limitx™ technology unique and visionary."

The National Institute on Drug Abuse (NIDA) from the NIH has awarded a \$300,000 grant to Acura for the phase I development of Limitx™ to optimize the formulation and make it ready for human testing. Additionally, interest from the FDA and NIH for oral abuse deterrent formulations is likely to encourage the creation of similar technologies and formulations by other manufacturers.

Acura plans to employ the Limitx™ technology in other opioids to expand its product portfolio. For instance, it is formulating Limitx™ using hydromorphone as its sole active ingredient. Hydromorphone is an opioid that is administered to patients with moderate to severe pain. Acura is also testing immediate-release hydrocodone bitartrate with acetaminophen (hydrocodone/APAP) tablets on the Limitx™ platform. With more than 135 million prescriptions dispensed in 2014 in the United States alone, hydrocodone/APAP is the most commonly prescribed opioid for pain management as well as the most commonly abused prescription opioid through excess oral consumption. Using Limitx™, Acura is expected to prevent the oral abuse of both these opioids and simultaneously enhance their functionality.

"One of the areas of focus for Acura is technology scalability. Through its proprietary Aversion® technology platform, it has formulated multiple abuse-deterrent analgesic opioids that cannot be easily crushed and snorted or injected into the body through a syringe," noted Verma. "It achieves this by employing an advanced hydrogel and polymer matrix drug delivery mechanism in its range of products. The effective scalability of its technology has allowed Acura to move on to its next-generation drug delivery platform, Limitx™."

Significantly, the company experienced exceptional growth in 2015 with revenue of \$5.4 million in the first quarter, compared to \$42,000 for the first quarter of 2014, registering a net profit of \$1.2 million. This growth was partly due to the licensing of one of the company's key products, Oxaydo™, to Egalet Corporation.

In the first quarter of 2015, Acura streamlined its focus on the Limitx™ platform. It has allocated \$1 million to the invention of formulations based on this platform to test the feasibility of the technology on other APIs and to ascertain its safety and efficacy. The complete commercialization of products based on the Limitx™ platform is still three to five years away.

Each year, Frost & Sullivan presents this award to the company that has demonstrated uniqueness in developing and leveraging new technologies that significantly impact both the functionality and the customer value of the new products and applications. The award lauds the high R&D spend toward innovation, its relevance to the industry, and the positive impact on brand perception.

Frost & Sullivan Best Practices Awards recognize companies in a variety of regional and global markets for demonstrating outstanding achievement and superior performance in areas such as leadership, technological innovation, customer service, and strategic product development. Industry analysts compare market participants and measure performance through in-depth interviews, analysis, and extensive secondary research to identify best practices in the industry.

Acura Pharmaceuticals is a specialty pharmaceutical company engaged in the research, development and commercialization of product candidates intended to address medication abuse and misuse, utilizing its proprietary LIMITX™, AVERSION®, and IMPEDE® technologies. LIMITX contains ingredients that are intended to reduce or limit the rate or extent of opioid release when multiple tablets are ingested. AVERSION contains polymers that cause the drug to gel when dissolved; it also contains compounds that irritate the nasal passages if the product is snorted. IMPEDE is designed to disrupt the processing of pseudoephedrine from tablets into methamphetamine.

OticPharma Acquires Novel Otitis Media Program from Otodyne, Inc.

PRNewswire: November 2, 2015 – IRVINE, CA, U.S.A., and REHOVOT, Israel – OticPharma, Inc., a privately held specialty pharmaceutical company focused on acquiring and developing innovative therapies for ear, nose, and throat (ENT) disorders, today announced that it has entered into a license agreement with Morristown, New Jersey based drug developer Otodyne, Inc., providing OticPharma with exclusive worldwide rights to develop and commercialize the company's investigational drug products for the treatment of otitis media and other conditions.

"We are extremely pleased to enter into this agreement with Otodyne, a company that has developed a truly novel approach to treating otitis media," said Gregory J. Flesher, chief executive officer for OticPharma, Inc. "The innovative approach focuses on restoring Eustachian tube function as a means to treat the underlying cause of otitis media. If successful, the approach could have broad reaching utility in children and adults."

Under the terms of the agreement, OticPharma will have responsibility for all development and commercialization activities. Otodyne will be eligible to receive a tiered royalty plus milestone payments based on successful development and commercialization of products worldwide.

"We are happy to partner with a company like OticPharma that has expertise in the development of novel products for the ear," said Alan Mautone, Ph.D., president of Otodyne, Inc. and authority on therapeutic surfactants. "We look forward to working with the company to continue the development of our investigational drug product and hope to someday bring this much needed product to patients."

"Otitis media is often painful and burdensome for patients and in chronic and severe cases frequently results in permanent hearing loss," said Sujana S. Chandrasekhar, M.D., chief medical officer of Otodyne, Inc., and leading otologist/neurotologist. "There are no FDA approved products that treat the underlying cause of otitis media, only resulting infections. More importantly, no FDA approved products can rapidly address the pain and pressure which is the primary reason patients seek medical attention. A safe and effective product that is fast-acting and free of antibiotics or steroids would be a significant improvement to the standard of care."

OticPharma, established in 2008, is a clinical-stage company active in the field of ear, nose, and throat disorders. The company's current product candidates are based on FoamOtic, a proprietary foam-based drug delivery system that provides sustained exposure of drugs.

Otic's lead product, FoamOtic Externa, is an investigational proprietary, foam-based, extended-release formulation of ciprofloxacin antibiotic, which has been designated for self-administration, once-daily to potentially treat acute otitis externa in minor and adult patients. The company recently completed a successful phase 2 clinical trial with FoamOtic Externa in minor and adult patients with acute otitis externa and is currently planning the phase 3 program.

October

U.S. FDA Approves BELBUCA™ (Buprenorphine) Buccal Film for Chronic Pain Management

PRNewswire: October 26, 2015 – DUBLIN, Ireland, and RALEIGH, NC, U.S.A. – Endo Pharmaceuticals Inc., a subsidiary of Endo International plc (NASDAQ: ENDP) (TSX: ENL), and BioDelivery Sciences International, Inc. (NASDAQ: BDSI) announced today that the U.S. Food and Drug Administration (FDA) has approved BELBUCA™ (buprenorphine) buccal film for use in patients with chronic pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. BELBUCA™, which is the first and only buprenorphine developed with a dissolving film that is absorbed through the inner lining of the cheek for chronic pain management, is expected to be commercially available in the United States during the first quarter of 2016 in seven dosage strengths, allowing for flexible dosing ranging from 75 to 900 µg every 12 hours. This enables physicians to individualize titration and treatment based on the optimally effective and tolerable dose for each patient.

"The availability of new, convenient, and flexible treatment options is important for patients whose lives are burdened by chronic pain, a debilitating condition that affects more Americans than diabetes, heart disease, and cancer combined," said Richard L. Rauck, M.D., director of Carolinas Pain Institute, Winston-Salem, NC. "BELBUCA™ provides a unique approach for chronic pain management, combining the proven efficacy and established safety of buprenorphine with a novel buccal film delivery system that adds convenience and flexibility. For both opioid-naïve and opioid-experienced patients who require around-the-clock treatment and for whom alternative treatment options are inadequate, BELBUCA™ offers appropriate, consistent pain relief and a low incidence of typical opioid-like side effects."

BELBUCA™ is a mu-opioid receptor partial agonist and a potent analgesic with a long duration of action that utilizes BDSI's patented BioErodible MucoAdhesive (BEMA®) drug delivery technology. Through this unique delivery system, buprenorphine is efficiently and conveniently delivered across the buccal mucosa (inside lining of the cheek). Buprenorphine is a schedule III controlled substance, meaning that it has been defined as having lower abuse potential than schedule II drugs, a category that includes most opioid analgesics. Among chronic pain patients taking opioids, the vast majority are on daily doses of 160 mg of oral morphine sulfate equivalent (MSE) or less. With seven dosage strengths up to 160 mg MSE, BELBUCA™ offers a treatment choice for a wide range of opioid needs in chronic pain sufferers.

"The FDA approval of BELBUCA™ represents an important and meaningful milestone for Endo Pharmaceuticals, demonstrating our strength in bringing a valuable new therapy from pipeline through approval. Our advancement of BELBUCA™ also underscores Endo's long-standing heritage of innovation and its commitment to supporting the pain community," said Rajiv De Silva, president and CEO of Endo. "We are proud to add BELBUCA™ to our diversified portfolio of branded and generic products and we look forward to preparing for the expected U.S. launch of the drug in early 2016."

The FDA approval of BELBUCA™ was based on two double-blind, randomized, placebo-controlled, enriched-enrollment phase 3 studies in patients with moderate to severe chronic low back pain. In these pivotal trials, a total of 1,559 opioid-experienced (study BUP-307) and opioid-naïve (study BUP-308) patients received the study drug. The trials included an open-label period in which patients were titrated to a tolerated, effective dose of BELBUCA™ and then randomized to either continue on BELBUCA™ or receive a placebo buccal film.

In both studies, BELBUCA™ demonstrated a consistent, statistically significant improvement in patient-reported pain relief at every week from baseline to week 12, compared to placebo. The most common adverse reactions (≥5%) reported by patients with BELBUCA™ in the clinical trials were nausea, constipation, headache, vomiting, fatigue, dizziness, somnolence, diarrhea, dry mouth, and upper respiratory tract infection.

"We are excited about the FDA approval of BELBUCA™, as we believe it is a testament to the strength of BDSI's partnership with Endo, and our ability to combine our expertise and resources to advance the available options in the treatment of chronic pain," said Dr. Mark A. Sirgo, president and CEO of BDSI. "BELBUCA™ is uniquely formulated with our BEMA® drug delivery technology that allows for high bioavailability of buprenorphine in the bloodstream, and represents an important new option for patients and healthcare providers." ■