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Newsletter

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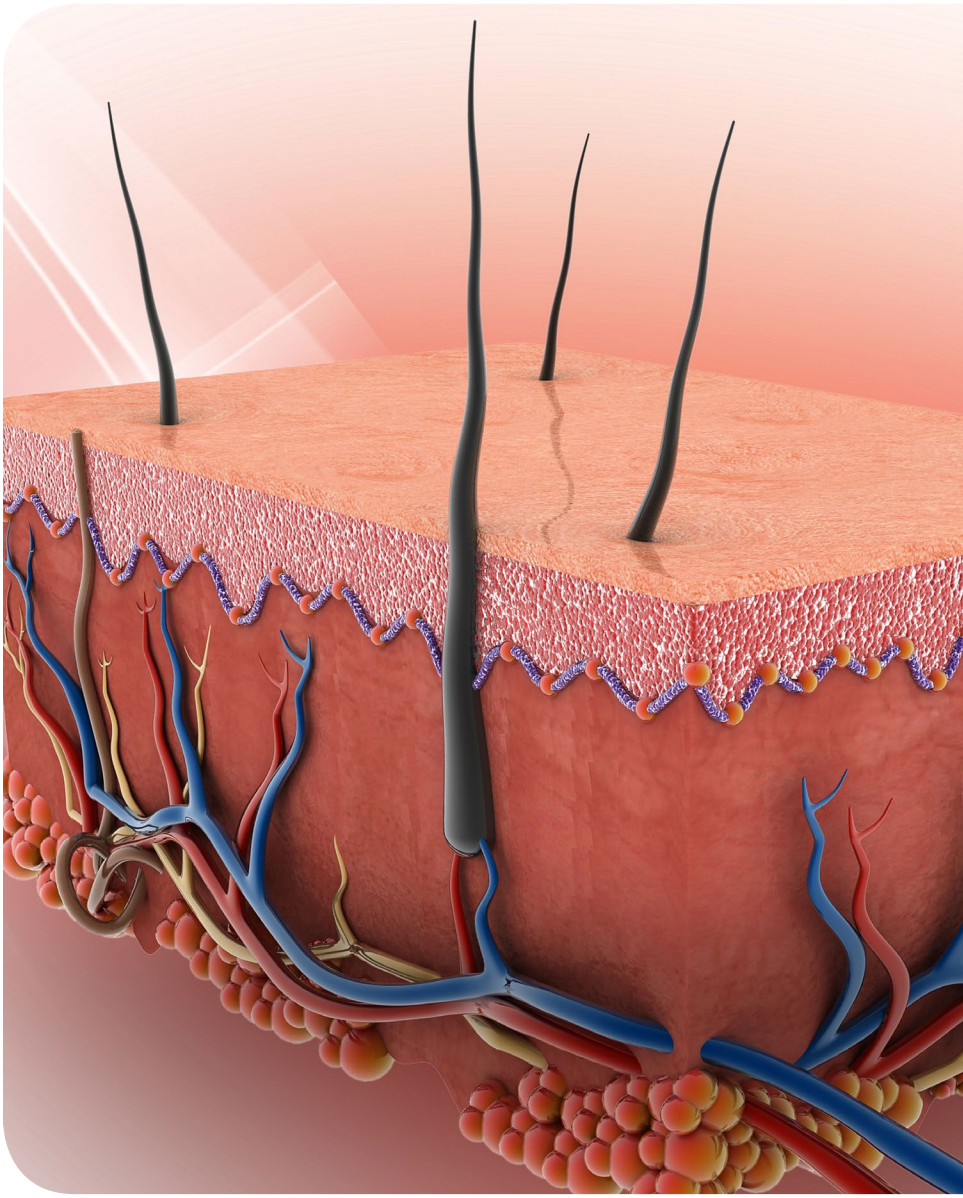

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The *CRS Newsletter* is the official newsletter of the Controlled Release Society. The newsletter is published six times annually, providing scientific and technical information pertinent to the controlled release community and news about society and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

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Steven Giannos
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Morning Meditation

Every morning I set aside 30 minutes for meditation and coffee. It gives me time to think about the day's activities, plan my day, and wake up with a nice hot cup of coffee. I used to drink tea, especially English Breakfast tea, but I switched to coffee in my mid-twenties. In 2004, I attended the CRS Annual Meeting in Hawaii, and after that spent a week at a coffee farm B&B in Kona. The coffee was delicious and I saw the actual coffee trees with berries. It was one of my more memorable trips and vacations.

I mention coffee because in this issue of the *CRS Newsletter* there is an interesting article about the use of coffee silverskin as a cosmetic ingredient. The coffee silverskin contains several classes of health compounds such as phenolics diterpenes, xanthines, and vitamin precursors. I would never think that this by-product would be investigated, and it is interesting to note that the coffee silverskin extract is being incorporated into skin treatments. As a transdermal scientist, I enjoyed reading this article and appreciate the new application of coffee silverskin to skin hydration and cosmetic formulations.

Another article in this issue describes the similarities in cancer disease and drug targets in dogs and humans. Terry Bowersock and Marilyn Martinez describe the growing recognition that spontaneous canine and human cancers share many features in common. Several examples are highlighted that show the similarities in human and dog cancers and serve as a model for research into related human cancers.

An additional article by Ali Seyfoddin *et al.* from New Zealand talks about patterned nanoporous polypyrrole (PPy) for tunable ocular drug delivery. Age-related macular degeneration (AMD) is one of the leading eye diseases in the world today. Getting medication to the posterior of the eye is fundamental in treating AMD. In this article, the authors describe the use of an ocular implant based on the conducting polymer PPy. Patterned nanoporous PPy films with ordered structures were successfully prepared and showed actuation upon oxidation and reduction, with the drug release being electrically tunable.

This issue's interview is with Hans Tromp of NIZO Food Research. His work in emulsion technology and using nanosized platelets to stabilize water-in-water emulsions will be the subject of an invited presentation at this year's CRS Annual Meeting.

There is also a report from the Spanish-Portuguese CRS Local Chapter detailing their Eleventh Annual Meeting, as well as a report from the Israeli Local Chapter and their first Young Israeli Controlled Release Society (YICRS) conference.

So, grab a cup of coffee and enjoy this issue of the *CRS Newsletter*.

Cheers,
Steven ■

Controlled Release in Foods: An Interview with Hans Tromp of NIZO Food Research

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

A fundamental element of emulsion technology is phase separation. Immiscible solvent systems such as oil-in-water or water-in-oil are commonly associated with these platforms due to relatively well-defined phase separations. Nevertheless, miscible systems can be manipulated to realize the phase separation needed to create functional controlled release emulsions. Hans Tromp's recent work, carried out together with Mark Vis of the University of Utrecht, using nanosized platelets to stabilize water-in-water emulsions will be the subject of an invited presentation at the 2016 CRS Annual Meeting this summer. This interview provides a glimpse of his work and an enlightening perspective on the use of controlled release in foods.

Q *What led you to a career involving controlled release?*

A My academic background is physical chemistry, in particular the properties of polymer solutions. The transition to food and encapsulation science happened naturally and turned out to be a move that made a lot of sense. My first encounter with controlled release was a fundamental study of the diffusion of water and other compounds in glassy polysaccharides.

Q *What is the scope of your current work in your organization?*

A NIZO food research is a contract research company providing innovative solutions to the international food industry. We were originally founded as a dairy research institute, but nowadays we work for food and ingredient companies worldwide. My role is to lead projects that translate physical–chemical fundamentals into real benefits for food products.

Q *What is the scope of controlled release in your work?*

A We execute controlled release projects in a broad range of areas, from tailored flavor release in chewing gum to pH-triggered release of probiotics in the human intestinal tract. It's a nice challenge for me to work within the requirements of food-grade materials and sensory qualities.

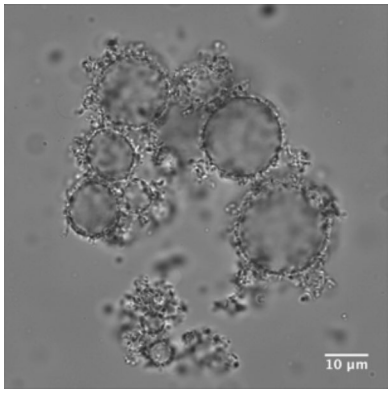
Q *What is the greatest controlled release challenge you have encountered? Were you able to address it?*

A A typical challenge for encapsulation in food systems is retention of payload during shelf life in uncontrolled conditions, such as temperatures in a car parked in the sun, while release remains triggered by consumption. I find inspiration in nature—often plants have developed solutions to such problems and, therefore, offer a direction in which a solution may be found. Examples are wax layers, pollen, and coffee beans.

Q *What will you be sharing at the 2016 Annual Meeting?*

A NIZO has been doing precompetitive research together with the University of Utrecht aimed at finding formulations for fully water-based liquid emulsions. These are emulsions that consist (typically) of droplets of protein-rich solution dispersed in a polysaccharide solution. There are many food-grade combinations of proteins and polysaccharides that are able to form such emulsions. Making them is easy, but stabilizing them demands a novel approach. This will be the subject of my presentation.

Apart from being potential substitutes for oil-in-water emulsions such as mayonnaise, fully water-based emulsions are expected to have interesting functionality as dispersed hydrophobic compound carriers for high bioaccessibility.



Droplets of a water–water emulsion stabilized by clay particles.

Q *Do you see other industries or application areas that could benefit from this technology?*

A This technology may be applicable in all areas of industry where there is a demand for replacement of solvents or oil by water for reasons of sustainability, biocompatibility, or healthier food.

Q *Do you foresee any potential for extensions or improvements for this technology?*

A The proof of principle of stabilizing fully water-based liquid emulsions against creaming and coalescence has been achieved using inorganic or composite biocolloid particles. Reaching the stage where food grade particles do the job is a matter of time. A considerable challenge remains stability against shear. The adsorption energy at water–water interfaces of basically anything, particles or molecules, is about a factor of thousand lower than in the case of oil–water interfaces. Therefore, shear will easily disrupt the stabilizing interface coating. The solution is some extent of interfacial gelation, such as enzymatic crosslinking the interfacial layer or interparticle bridging with an adsorbing polymer. ■

Similarities in Cancer Disease and Drug Targets in Dogs and Humans

Terry Bowersock[a] and Marilyn Martinez[b]

Overview

"One Health" refers to the interconnection of health of humans, animals, and the environment. Scientists, doctors, and veterinarians working together can improve health for everyone. One example is controlling and treating cancer. Cancer is the number two cause of death in humans in the United States. Cancer accounts for almost half of the deaths of pet dogs over 10 years of age. Dogs get cancer at roughly the same rate as humans, while cats get fewer cancers. Common cancers in dogs include hemangiosarcoma, mast cell tumors, lymphoma, melanoma, breast cancer, and osteosarcoma (www.wearethecure.org/more_cancer_facts.htm).[1]

There is a growing recognition that spontaneous canine and human cancers share many features in common, including histology, resistance/recurrence, and metastasis.[2] Accordingly, there are many benefits to using naturally occurring pathologies that cannot be derived through the use of *in vitro* and rodent-based approaches. Cell cultures are highly controlled and allow for highly repeatable conditions to evaluate cancer growth and therapeutics. However, cell cultures are two dimensional, in contrast to the much different three-dimensional tumor "shapes" within humans. Defining the response of cells and using this to predict behavior of drugs *in vivo* are very difficult. Alternatively, use of rodent xenograft cancer models can fail to accurately predict the interaction between therapeutic agent and the cancer cells. Prediction errors can reflect the failure of these xenographs to develop the blood flow characteristics that occur in the natural host, where tumors grow in a variety of different solid tissues. Furthermore, because the murine model involves immunocompromised mice, the role of the immune system in tumor progression and drug response cannot be evaluated. Genetically engineered mice have also been used to induce tumors. While an improvement over cell cultures and xenograph in predicting drug response in the targeted host, differences in genetic and phenotypic expression of the tumor can interfere with translation of drug response to human disease. Mice also have a much a higher tolerance to cytotoxic agents compared with that seen in humans. Hence, only 8% of therapeutics have been successfully transferred from rodents to humans.[3,4]

The dog's response to therapeutic agents is similar to how humans respond to cytotoxic agents and has been demonstrated to be an outstanding model for exploring potential therapeutic solutions to human cancers. Examples include the utility of bone marrow transplantation (with cyclophosphamide) for the treatment of lymphoma, the effectiveness of antiangiogenic thrombospondin-1-peptide mimetics (with or without chemotherapy) for the treatment of non-Hodgkin's lymphoma, and the effectiveness of GS-9219, a prodrug of the nucleotide analogue 9-(2-phosphonylmethoxyethyl) guanine (PMEG), that delivers PMEG and its phosphorylated metabolites to lymphoid cells and exerts a cytotoxic effect on cells with a high proliferation index.

Underlying the use of dogs in the advancement of cancer therapy is the similarity in the growth, tissue origin, and molecular characteristics of the disease, reflecting the greater genome similarities in dogs and humans versus mice.[3] For example, similarities in molecular targets have been shown in tumor suppressor p53, breast cancer type 1 (BRCA1), tyrosine protein kinase Kit (c-Kit/CD117), cytoplasmic-myelocytomatosis oncoprotein (c-Myc), Kirsten rat sarcoma viral oncoprotein (K-RAS), and many more. In addition, the regulatory requirements for registration of a new therapeutic are less time consuming for animals, providing an opportunity for immediate benefit to dogs while paving the way for future registration in humans.[3,4]

Commonality of Disease

Lymphoma: The rate of increase in certain cancers (such as lymphomas) has doubled in dogs over the past 40 years, a rate that is similar for the increase in non-Hodgkin's lymphoma in people.[3,4] Lymphomas in dogs are similar to non-Hodgkin's lymphomas in humans in epidemiology and biology, including molecular characteristics as well as clinical manifestations. RNA sequencing with

continued

[a] Zoetis, LLC (formerly Pfizer Animal Health), U.S.A.
[b] U.S. Food and Drug Administration, U.S.A.

microarray analysis confirmed numerous molecular similarities between canine lymphomas and human non-Hodgkin's lymphoma. These included the PI3-K/Akt/mTor pathway. The B-cell lymphomagenesis signaling system including CD19, PI3, MYC, and GSK3® along with LYN and SYK, tyrosine kinases involved in B-cell signaling, and cross talk with the PI3/Akt signaling pathway have also been identified in canine lymphoma cells. The PSME1/2 proteasome activator and NFkB activity were also identified in canine lymphoma. There is also evidence that infectious agents such as Epstein–Barr virus (EBV) may play a role in canine lymphoma in a manner similar to non-Hodgkin's lymphoma in humans, because a majority of dogs have serological titers to EBV. Furthermore, there is currently no evidence of PI3 kinase or pAkt activity in lymph nodes from dogs without lymphoma, further confirming the role of these pathways in the disease state. These findings strongly support the use of dogs as a translational model to study the genetic basis of lymphoma in humans as well as evaluation of potential therapeutic strategies.[5]

Malignant melanoma: Malignant melanoma is one of the most common cancers in both dogs and humans. In dogs, canine malignant melanomas (CMM) are often associated with oral mucosa, whereas in humans metastatic melanomas (HMM) are found in the skin. There is a high fatality rate for human and canine melanoma patients, and the tumors are resistant to all forms of therapy for both host species. As for lymphomas, PI3/Akt signaling pathways are common in both CMM and HMM. Furthermore, there are genetic similarities seen in cancer of dogs and humans. Similarities are also seen in the micro-RNA (miRNA) involvement in dog and human disease progression (cell growth and oncogenesis). In disease and health, miRNAs are typically involved in a negative regulation of gene expression, with each miRNA controlling hundreds of genes. This is true in cancer as well, where miRNA can regulate cell replication. This prompted the study of adding exogenous made miRNAs to down regulate sites of binding of oncomirs (miRNAs involved in cancer) to reduce growth of abnormal cells. Mir-203 and Mir-205 were found to target gene *erbb3* of the EGFR tyrosine kinase receptors, thereby reducing cell growth of malignant melanoma cells in dogs and humans. This is another example in which the dog can serve as a translational model to study melanoma in humans.[6]

Osteosarcoma: Osteosarcoma is an aggressive tumor of bone. Although progress has been made in therapy for primary osteosarcoma tumors (OSA), treatment of metastases is much less effective, and the targeting of resistant cells within metastatic tumors is a primary goal of ongoing research. Primary and metastatic OSA is also found in dogs. Genetic analysis of 30 primary osteosarcoma tumor samples in humans and dogs could not be divided by species, suggesting that similarities in gene expression signatures in osteosarcoma are due primarily to shared biology across species. For example, recent studies have found that dogs and humans share expression of BMI1, a member of the c-Myc receptor complex of transcriptional regulation. BMI1 is integral for self- renewal capacity of normal and cancer stem cells. BMI1 is essential for OSA growth in humans, metastatic activity, and resistance to therapeutic drugs in humans. Similar characteristics have been confirmed for canine OSA. BMI1 has also been confirmed to be expressed in metastatic tumors in both dogs and humans. Small molecules that inhibit BMI1 expression in human OSA work in a similar manner in dogs. These small molecules, as well as siRNA, work together with chemotherapeutic agents to reduce growth of OSA cells *in vitro*. BMI1 has also been suspected as being a key factor in stimulating cancer stem cell replication in both dogs and humans. These shared characteristics make dogs an ideal large animal model to evaluate the progression and control of OSA in humans.[2,7]

Concluding Thoughts

These examples show the value of using naturally occurring canine cancer as a model and integral part of research into similar human cancers. Importantly, a wide range of therapeutics has been rapidly advanced for human use by studies conducted in canine cancer patients. Based upon an examination of progress in the treatment of the various shared cancers, it was concluded that studies conducted in the dog (in conjunction with an appreciation of species-associated similarities and differences) have resulted in faster go/no-go decisions, along with the identification and validation of biological endpoints and surrogate markers critical to quick translation into phase I and phase II human clinical trials.[2]

Pet animal studies provide support of the mechanistic pathway. Studies that would be difficult to complete in humans, including multiple biopsy and collection time points, are feasible in pet animal studies and can lead to improvements in the design of human clinical trials (e.g., treatment schedules, drug combination strategies, effect of chronic drug exposures, and an assessment of potential correlative and surrogate endpoints).[8] In the third and final article in this series, the use of dog models in developing delivery systems to treat cancers will be discussed.

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An Overview of Coffee Silverskin Validation as a Cosmetic Ingredient

Francisca Rodrigues[a] and M. Beatriz P. P. Oliveira
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Over the past decades, demand for natural resources has accelerated to the extent that it is now widely considered a serious threat to the proper functioning of economies and societies owing to associated environmental problems such as climate change, biodiversity loss, desertification, and ecosystem degradation.[1] At a time when eco-consumerism is increasingly focusing end-user attention on all aspects of products, including raw material sourcing, manufacturing, and disposal, the beauty product sector has been accused of numerous environmentally unfriendly practices.[2] Within the rapidly growing market for personal care products, a number of analyses show that the highest environmental impact of cosmetic products is at the consumer level, where consumer concerns range from unsustainable sourcing of raw materials, to pollution (both in the manufacturing phase and the disposal of packaging and products) and animal testing.[2] In response, companies have attempted to address these issues holistically by focusing on sustainable raw material sourcing and greener formulations.[2] However, these laudable practices face both consumer skepticism, which often views these activities as "green washing," and the reality of the market, because in a global economy there is little desire for premium pricing to cover the increased costs of these products compared with conventional products. Agro-industrial by-products have the potential to be used for different purposes, providing economic advantage over other disposable residues.[3] In particular, the field of skin care products and cosmetics may benefit from these remaining materials.[3] Few studies report possible uses for agro-industrial wastes. Human skin is a complex organ that regulates body heat and water loss, while preventing the entry of toxic substances and microorganisms. Natural ingredients, phytonutrients, microbial metabolites, dairy-derived actives, minerals, and animal protein components have long been believed to benefit healthy skin aging. Indeed, from a sustainable point of view, this new application could provide in the near future a method of recycling for food companies, developing cost-efficient processing methods, decreasing the negative impacts of wastes on the environment, and providing other economic advantages for companies.

Coffee is one of the most popular beverages of the world and the second most traded commodity.[4] Usually, each coffee fruit contains two coffee beans, each one covered by a thin, tight skin called silverskin.[5] Coffee silverskin (Figure 1) is obtained after roasting coffee beans; it is completely removed during coffee beverage production. This by-product has no commercial value, being normally discarded as a solid waste.

Figure 1. *Coffee silverskin.*

Recent advances in industrial biotechnology lead to potential opportunities for economic valorization of this by-product.[6] Different authors have intensively studied this coffee by-product. Regarding its macronutritional composition, is well documented to contain high amounts of dietary fiber (50–60%, including 85% soluble fiber and 15% insoluble fiber), protein (16.2–19%), and minerals (4–5%).[7–9] However, the exact mineral composition of coffee silverskin has not been clarified.[10] The high antioxidant capacity of coffee silverskin, particularly in chlorogenic acid, probably owing to the concentration of phenolic compounds, has also been detailed.[7,11–14] Also, the caffeine content is high and similar to that of coffee beans.[11–12] These compounds are believed to provide *in vivo* protection against free radical damage. As with coffee beans, coffee silverskin contains several classes of health compounds such as phenolics, diterpenes, xanthines, and vitamin precursors.[15] However, few studies reported the use of by-products as antioxidant sources for the cosmetic field.[3,13,16–19] According to these research studies, the majority of these antioxidants are polyphenols and isoflavones. **The question is, how can we validate coffee silverskin as a new cosmetic ingredient, particularly as an anti-wrinkle ingredient?**

Recent changes in regulatory requirements and social views on animal testing have prompted the development of reliable alternative tests for predicting skin and ocular irritation potential of products based on new raw materials. Nevertheless, to guarantee the safety of these new ingredients, stability and toxicity assays should be performed to avoid the presence of irritating constituents. Rodrigues *et al.* evaluated the cytotoxicity of coffee silverskin in monolayers of different skin cell lines.[13] No cytotoxicity was observed. Also, a number of *in vitro* three-dimensional models have been developed to assess potential skin or eye irritants by the cosmetics industry, such as the

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reconstructed human epidermis test (EpiSkin™) and the human corneal epithelial model (SkinEthic™ HCE), respectively. The same research group performed these assays in three different extracts of coffee silverskin. The histology of the models after extract application was also analyzed. The *in vitro* results demonstrated that extracts were not classified as irritants, and the histological analyses proved that extracts did not affect either model's structure. The contents of caffeine, 5-hydroxymethyl furfural, and chlorogenic acid were quantified after the epidermal assay, proving that caffeine was in a similar amount to coffee beans. Thus, this new extract could clearly be used as an anticellulitis agent.

The *in vivo* test carried out with the most promising extract (hydroalcoholic) showed that, with respect to irritant effects, it can be regarded as safe for topical application, because no skin irritation was observed.

Rodrigues *et al.* also incorporated coffee silverskin into different cosmetic formulations, such as a body cream and a hand cream.[19–20] *In vitro* results were completely satisfactory, as no toxicity was observed in keratinocytes nor in fibroblasts. Also, the *in vivo* assays demonstrated that both formulations were safe. The sensorial analyses performed with volunteers demonstrated complete satisfaction with both products. Recently (data not available) a facial formulation with coffee silverskin (formulation A) and the same cream enriched with hyaluronic acid (formulation B) were compared *in vivo*. Formulations were applied twice a day by volunteers (n = 20 for each formulation) during 28 days. The influence on skin hydration and viscoelastic properties was investigated with validated devices (Corneometer® and Cutometer®). Wrinkle depth, roughness, volume of cavities, and Visioface® images were analyzed at time 0 and after 28 days. Volunteers were asked about efficacy perception. Results revealed that permeation of coffee silverskin extract in pig ear skin after 8 h was about 20%. No cytotoxicity was observed for both formulations. Significant changes in skin hydration and viscoelastic parameters were detected for both formulations, without differences between formulations. However, no differences were observed regarding wrinkle depth, roughness, and volume of cavities for both formulations (Figure 2). Coffee silverskin represents an effective ingredient for cosmetic creams that are intended to increase skin hydration and firmness, with no *in vivo* differences regarding hyaluronic acid.

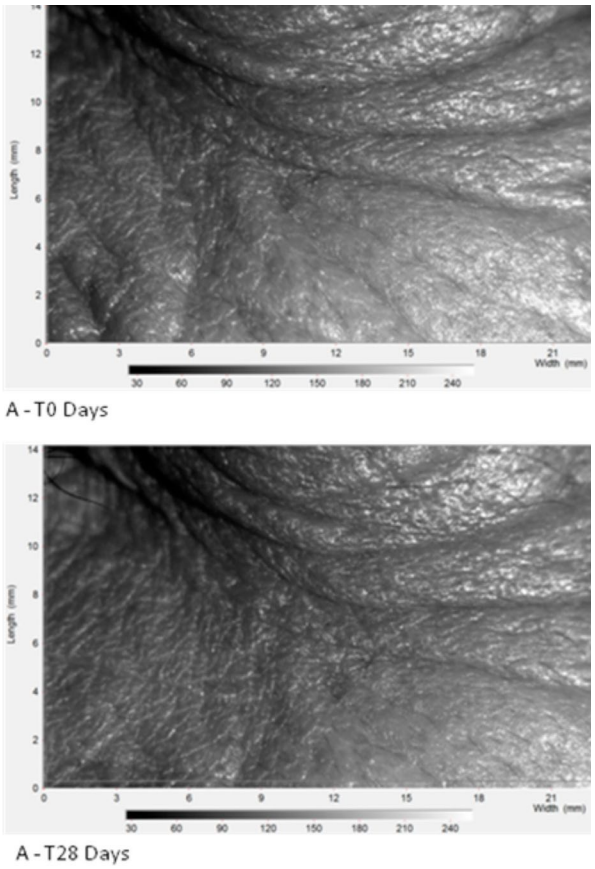

Figure 2. *Photography of the periocular area (acquired with PRIMOS™ equipment) of one of the volunteers who exhibited reduced depth of wrinkles at time 0 and after 28 days of treatment.*

In the same context, the potential for nanostructured lipid carriers loaded with caffeine, obtained from coffee silverskin, as a new approach for topical therapy of cellulitis, has been investigated in our group with interesting results (data not available).

Acknowledgements
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Patterned Nanoporous Polypyrrole for Tunable Ocular Drug Delivery

Ali Seyfoddin,[a,b] Hongrui Zhang,[c] Simon Moulton,[c] Michael Higgins,[c] Ilva Rupenthal,[d] Geoff Waterhouse,[e] and Darren Svirskis[a]

Introduction

Corticosteroids such as dexamethasone are the first line of treatment for noninfectious posterior uveitis and are also routinely used for the treatment of age-related macular degeneration (AMD) (Figure 1). However, there are several issues with the current treatment: there is low ocular bioavailability following systemic or topical administration, and bimonthly intravitreal injections are associated with complications such as endophthalmitis. Our solution is an ocular drug delivery implant based on the conducting polymer polypyrrole (PPy).

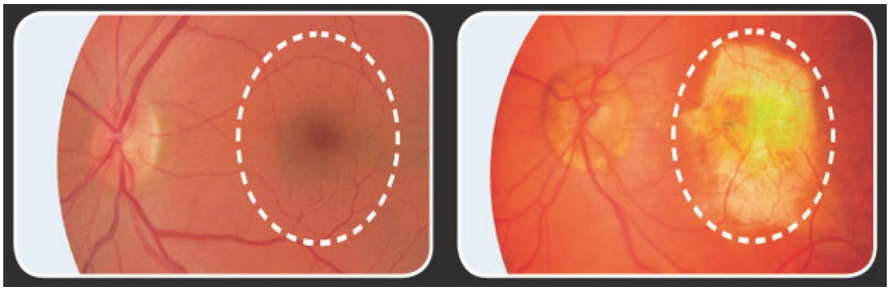

Figure 1. *Photograph of normal retina (left) and abnormal retina with AMD (right).*

Conducting polymers such as PPy offer the advantage of being biocompatible in addition to other intrinsic properties such as being responsive to electrical stimuli and easily fabricated. PPy is prepared by either chemical or electrical polymerisation and has been widely investigated for smart technologies. To achieve both sufficient drug loading and electrochemical sensitivity, three-dimensionally ordered nanoporous films that are electrochemically grown on a sacrificial template offer an extended internal surface area for increased drug loading and effective ion exchange.[1] In comparison to conventional PPy films, nanoporous PPy structures are expected to have reversible wettability, higher conductivity, improved ion exchange, higher surface area, and higher solid volume fraction.[2] To demonstrate the applicability of conducting polymers for on-demand ocular drug delivery, dexamethasone sodium phosphate (DexP), an anti-inflammatory corticosteroid, was incorporated into nanoporous PPy. Figure 2 illustrates the microfabrication. Dexamethasone is used in the management of AMD and diabetic macular oedema, for which a controlled release on-demand implantable device would be extremely beneficial.

Experimental Methods

A polymethyl methacrylate (PMMA) sacrificial template was deposited by a vertical method (Figure 2). Electrochemical polymerisation of PPy was achieved by a three-electrode galvanostatic method. The electrochemical solution contained 0.1M pyrrole and 0.1M *p*-toluene sulphate. For release studies, DexP (the negatively charged water-soluble form of dexamethasone) was used as the dopant from a solution containing 0.05M DexP and 0.2M pyrrole with the pH adjusted to 3 using 0.1M HCl. After polymerisation, the PMMA colloidal crystal template was selectively dissolved by immersion in a

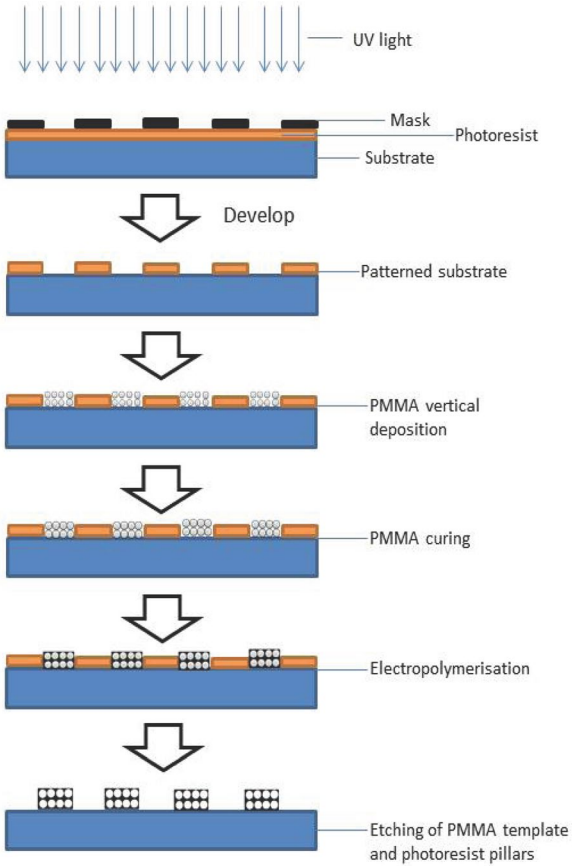

Figure 2. *Microfabrication of nanoporous PPy-DexP films.*

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toluene/acetone mixture (1:3, v/v) for 24 h. The morphology of the structures was studied with scanning electron microscopy (SEM), optical properties with reflectance spectroscopy, and electrochemical properties with impedance spectroscopy. Drug release studies from the nanoporous PPy structures were carried out in a three-electrode electrochemical setup in phosphate buffer (pH 7.4). Following 24 h passive release, electrical stimulation was applied for 60 min at 24 and 48 h by pulsing the potential to ±0.6 V.

Results and Discussion

The SEM image (Figure 3) displays the interconnected nanoporous PPy structures fabricated. UV-Visible reflectance spectroscopy was used to investigate electro-actuation (Figure 4C). The oxidised PPy structures had a photonic bandgap at 600 nm and exhibited a green colour. On reduction, the photonic band gap shifted to longer wavelengths (725 nm), exhibiting a red colour, which indicates a decrease in interplanar spacing in the nanoporous PPy and thus decreased internal void volume (Figure 4). The net movement of ions in and out of the polymer allowed for electrical control over PPy actuation. The decrease in interplanar spacing observed upon reduction would result from deswelling of PPy, indicating the predominant anion-driven actuation for this system.

The nanoporous PPy, which can also be described as an inverse opal (IO), had slightly lower impedance than the conventional films, owing to increased fluid flow into the bulk of the polymer resulting in more efficient ion exchange.[3] The influence of electrical stimulation on release is clearly evident in Figure 5. Interestingly, and particularly following the first period of electrical stimulation from the nanoporous PPy structures, the increased release rate extended for at least 2 h after termination of the electrical stimulus. Electrical stimulation is able to mobilise the dopant within the polymer structure, and movement of DexP closer to the polymer–media interface is expected to result in increased passive release after the electrical stimulation is stopped.

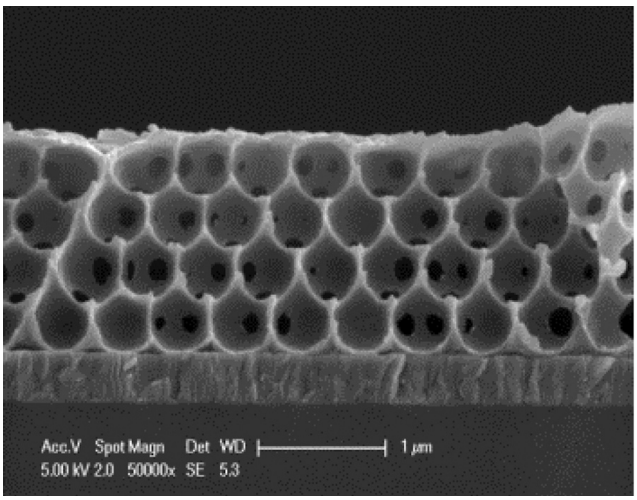

Figure 3. *SEM cross section of a nanoporous PPy pillar.*

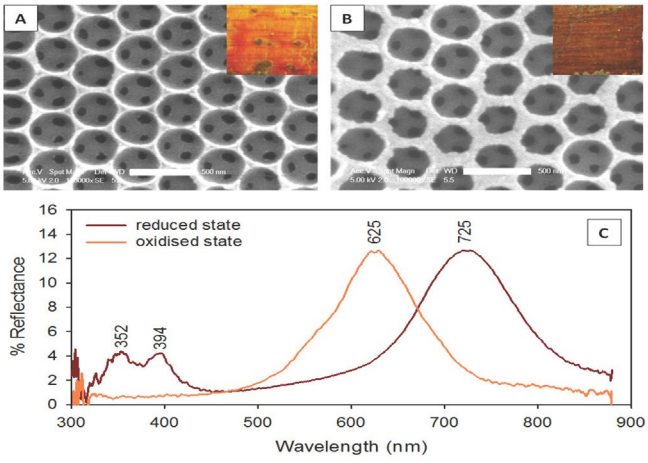

Figure 4. *(A) SEM image of nanoporous PPy film at reduced state. (B) SEM image at oxidised state. (C) UV-Vis reflectance spectra collected in air at normal incidence from the oxidized and reduced nanoporous PPy film. © Elsevier; reproduced by permission.[4]*

Conclusion

Patterned nanoporous PPy films with ordered structures were successfully prepared and showed actuation upon oxidation and reduction, with the drug release from these films being electrically tunable. Such films could be utilized in the development of electro-stimuli responsive ocular implants that allow dose individualisation.

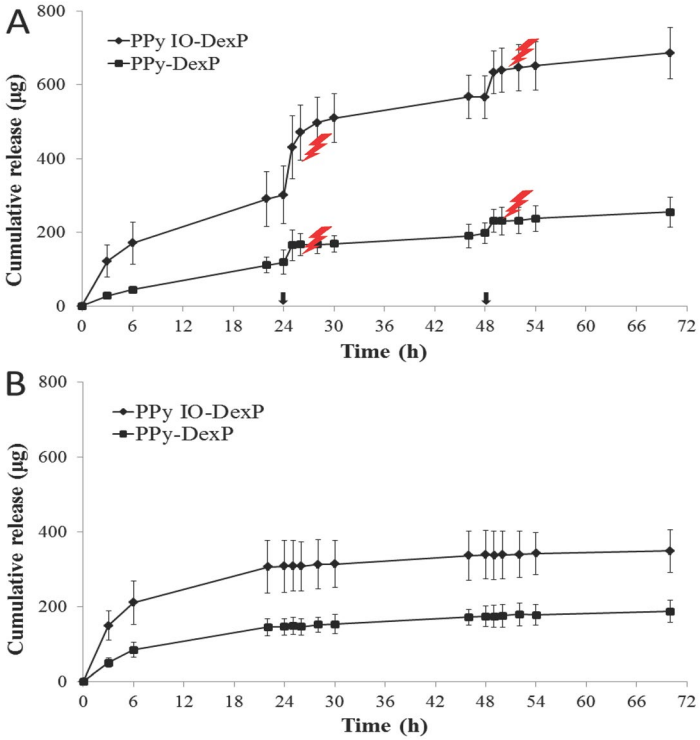

Figure 5. *(A) Triggered drug release profiles for the nanoporous PPy-DexP (labeled PPy IO-DexP) film versus conventional PPy-DexP film. (B) Passive drug release profiles. © Elsevier; reproduced by permission.[4]*

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Acknowledgements
The authors thank Andrew Chan for his assistance with the UV reflectance and angled resolved UV-Vis measurements, Sina Jamali for impedance studies, and Naveed Yasin for his help with the HPLC. We also thank the University of Auckland's Faculty of Medical and Health Sciences Research and Development Fund and the PJ Smith Freemasons for financially supporting this project. A complete version of this work is published in the *European Journal of Pharmaceutics and Biopharmaceutics*.[4]

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CRS Premeeting Workshop on the Regulatory Landscape for Therapeutic Biologics

Kinam Park, Purdue University, U.S.A.
Chair of the 2016 CRS Annual Meeting

Overview
While some biologics are intended to treat diseases and medical conditions, others are designed to prevent or diagnose diseases. The therapeutic biological products (TBPs) regulated by the Center for Drug Evaluation and Research (CDER) of the U.S. FDA typically refer to the following:

- Monoclonal antibodies for *in vivo* use
- Proteins intended for therapeutic use, including cytokines, growth factors, enzymes, thrombolytic proteins, and other novel proteins
- Immunomodulators
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease, or otherwise alter the production of hematopoietic cells *in vivo*.

Other biologics such as vaccines, blood, and gene and cell therapies are regulated by the Center for Biologics Evaluation and Research (CBER) of the U.S. FDA.

The workshop is aimed at providing a snapshot of the recent evolution in product development and regulatory evaluation of therapeutic biologics. In addition to therapeutic biologics, the workshop will also introduce the regulatory considerations for complex drug substances including peptides, which typically have no more than 40 amino acids, as well as related drug delivery systems such as implants and microspheres for parenteral administration.

Recognizing the challenges associated with developing and evaluating biological products, both governmental entities and industry in different regions of the world have made considerable efforts to do this right. This workshop will present several case studies covering both product development and regulatory evaluation of biological drug products. The goal of the workshop is to provide recent information related to global efforts on developing regulatory approaches to ensure smooth and efficient evaluation and approval of biological drug products. Contributors consist of current and past regulatory experts from both the United States and Europe.

The co-chairs, Hong Wen and Yan Wang, prepared this exciting workshop by assembling a great team of experts from around the world. The invited speakers include John Petricciani, Serge Beaucage, Liang Zhao, Mohan Sapru, Audrey Jia, Evangelos Kotzagiorgis, Xiaohui Jiang, Harsh Jain, Yan Wang, and Wen Qu. Below are synopses of a few presentations.

Complex Drug Substances Including Peptides
Drug products containing complex drug substances have unique therapeutic profiles that small molecular drugs cannot replicate. Complex drug substances can be a single molecule or a mixture of different components, and these include natural products, peptides and conjugated peptides, synthetic and biopolymers, and any other drug substance that presents a challenge in its characterization. Regulatory considerations differ slightly for drug products under a New Drug Application (NDA) and an Abbreviated New Drug Application (ANDA). Characterization including elucidation of structure and other characteristics is the main focus for complex drug substances in the NDA process. Although it still serves as the foundation in an ANDA containing a complex drug substance, the goal of characterization in an ANDA is to demonstrate the sameness of the active ingredient or pharmaceutical equivalence between a reference listed drug (RLD) and the proposed generic drug products. Nevertheless, having good characterization of a complex drug substance is a critical step to gain regulatory approval under either the NDA or ANDA path. In recent years, advances in analytical techniques contributed to the success of a number of NDA and ANDA products. The presentation will highlight regulatory considerations on characterization of complex drug substances including peptides using the advanced analytical techniques.

Therapeutic Biological Products
Different from structurally well-defined, low-molecular-weight chemical drugs, biologic products are complex molecules that are generated from live cells, such as bacteria, yeast, or mammalian cells. Most of them carry post-translational modifications (PTM) and have inherited heterogeneity. They often contain multiple units/domains and have multiple functions and a complicated mechanism of

Special Feature continued

action (MoA). Their manufacturing processes are also more complicated than synthetic small molecules. In addition, biological products often have immunogenicity issues when used in patients.

Nowadays, the pharmaceutical and biotechnology industry has invested significantly in the development of "biosimilars." However, in addition to the challenges listed above, the developers often need to use different cell expression systems, raw materials, processes, purification platforms, and different formulations during product development. The unpredictable manufacturing differences and limited knowledge on the variation of the reference products make development of successful biosimilars challenging. The presentation aims to provide a road map facilitating the development of biosimilars from an industry perspective.

Gene and Cell Therapies

There will be two presentations focusing on amphipathic trans-acting phosphorothioate DNA elements to deliver uncharged peptide nucleic acids (PNAs) and phosphorodiamidate morpholino oligomers (PMOs) as well as negatively charged DNA and RNA sequences in mammalian cells. Most human genes undergo alternative splicing events, which are triggered by intricate and highly regulated machinery requiring the sequence-specific binding of several proteins to nuclear pre-messenger RNAs (pre-mRNAs). Steric interference imparted by RNase H-incompetent oligonucleotide analogues, complementary to specific pre-mRNA splice sites, has been shown to be efficient at redirecting the splicing machinery during assembly of mature mRNAs.[1] Indeed, skipping the mutated exons in dystrophin pre-mRNA, as an approach to the clinical treatment of Duchenne muscular dystrophy, highlights the biomedical significance of alternative splicing events.[2]

Nucleic acid–based drugs have been recognized as powerful tools for targeting therapeutically important mRNAs and eliciting their destruction or preventing their expression into protein-causing diseases. By virtue of their gene silencing properties, nucleic acid–based drugs have tremendous potential in the treatment of cancer, infectious diseases, and "undruggable" diseases in humans. However, a major impediment to the therapeutic application of nucleic acid–based drugs is *in vivo* delivery; a primary reason for this is the polyanionic nature of nucleic acids, limiting their cellular internalization. Nucleic acids can be divided into two categories on the basis of their sizes. DNA plasmids and mRNAs belong to the high-molecular-weight category, whereas siRNAs, antisense oligonucleotides, DNA or RNA aptamers, and DNA decoys (to name a few) belong to the low-molecular-weight category. Both categories present unique challenges, in terms of delivery, based on the number of negatively charged phosphodiester functions available for electrostatic interactions with cationic delivery reagents.[3]

Cell-based medicines (cell therapies, or CTs) are among the most recent new biologicals. They are complex in their structure, content, mode of action, and delivery. In addition, there is substantial diversity among CT products, and their nonclinical and clinical testing programs will depend on product-specific features and their clinical indications. All of these factors create significant challenges for regulators and developers of CTs. Nevertheless, the CT field has advanced rapidly during the past decade, and products already have been approved in several countries. It remains an emerging area of biomedical research and development in which there are many areas of regulatory uncertainty and differences among countries and regions. The presentation will focus on the recent advances in the international regulatory landscape for cell therapy.

To register for this workshop, being held on Saturday, July 16, 2016, and for more information on the CRS Annual Meeting, visit controlledreleasesociety.org/meetings.

Disclaimer

This article reflects the views of the author and should not be construed to represent the FDA's views or policies.

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How the First Young Israeli Controlled Release Society (YICRS) Conference Was Established

Assaf Zinger, Technion, Israel

My name is Assaf Zinger, and I am a Ph.D. student in Avi Schroeder's lab at the Technion, Israel. I'd like to share with you the story of the first YICRS conference.

So, like any other good story, "Once upon a time in faraway place…" Actually, it was on July 24–25, 2015, at Tel Aviv University. I was sitting behind Dan Peer, president of the CRS Israeli Local Chapter, during a CRS-sponsored conference: "New Horizons in Nanomedicine." After enjoying all the amazing lectures, one thing started to disturb me: the fact that not even one student asked a question! So, during the coffee break I spoke with three professors—Dan Peer, Avi Schroeder, and Roey Amir—and shared my thoughts with them. I wanted to get students involved. Luckily for me, they also agreed. The next step was to put together an amazing team of people to make my idea come to reality. Tsuf Croitoru, Michal Shevach, Zvi Yaari, Maya Bar-Zeev, and I became the organizing committee of the first YICRS Conference.

Dan Peer, president of the Israeli Controlled Release Society, together with the first YICRS Conference organizing team. Left to right: Dan Peer, Michal Shevach, Maya Bar-Zeev, Assaf Zinger, Tsuf Croitoru, and Zvi Yaari.

The purpose of the conference was to share and spread knowledge. We encouraged the participants to be involved, to ask questions during the lectures, and to mingle during the breaks. The conference drew 106 students from all over the country: Haifa, Tel Aviv, Jerusalem, and Be'er Sheva. Before the conference we asked students to submit work they wanted to present, and out of many great candidates, we chose 24 excellent research topics to highlight.

We were glad to also have two plenary speakers: Alon Seri-Levy, the CEO of Sol-Gel Technologies, discussed how to turn controlled release technology into products, and Dan Peer (Tel Aviv University) shared with us his experience of working with a concept to a novel clinical modality. These tangible examples were extremely motivating and inspiring to many of the scientists in the room.

The conference was divided into four different sessions, covering RNA/ DNA delivery systems and imaging, controlled delivery systems and tissue engineering, nanoparticulate delivery systems, and targeted delivery systems.

Conference participants.

Throughout the day we received fantastic feedback from the students, who said that the freedom of being able to ask questions to a peer without feeling embarrassed really helped them to learn. We were happy to see that some students even started collaboration ideas between universities, something that is crucial in our field of research. At the end of the day, five speakers were awarded for best presentations—which was hard to do because we had so many talented researchers and exciting ideas!

It was an amazing experience, and we are already looking forward to the second YICRS conference. ■

Eleventh Annual Meeting of the Spanish-Portuguese CRS Local Chapter

José L. Arias,[1] Emilia María Barcia,[2] and María Adolfina Ruiz[1,3]

The 11th biannual meeting of the Spanish-Portuguese CRS Local Chapter (SPLC-CRS) was held January 21–23, 2016, at the Ilustre Colegio Oficial de Farmacéuticos de Granada in Granada, Spain. The 122 participants included seven scientists from industry, 108 scientists from academia (of which 71 were students), four clinicians, and three representatives from governmental offices. The meeting was sponsored by CRS, SPLC-CRS, the University of Granada, the Faculty of Pharmacy of the University of Granada, the Ilustre Colegio Oficial de Farmacéuticos de Granada, and the Hermandad Farmacéutica Granadina (Hefagra S. Coop. And.), which allowed the organizers to invite outstanding scientists from industry, regulatory agencies, and academia as well as clinicians to present recent developments and rising trends in the converging fields of pharmacy, nanotechnology, biotechnology, and medicine, thus providing a platform for both multidisciplinary communication and new cooperation to participants from both industry and academia. The conference provided a complete overview into the state of the art in those fields, and it also allowed learning about the research done and the latest results. The discussion on recent advances, difficulties, and breakthroughs was at the highest level.

The opening ceremony.

The 11th Spanish-Portuguese Conference on Controlled Drug Delivery: Revolutionary Approaches in Nanomedicine Development was opened by Pilar Aranda Ramírez (rector of the University of Granada), Ana del Moral García (dean of the Faculty of Pharmacy of the University of Granada), Antonio Mingorance Gutiérrez (president of the Consejo Andaluz de Colegios Oficiales de Farmacéuticos), Manuel Fuentes Rodríguez (president of the Ilustre Colegio Oficial de Farmacéuticos de Granada), and María Adolfina Ruiz Martínez (president of SPLC-CRS), who warmly welcomed the participants, giving also a brief introduction on the conference program. Briefly, the program included four plenary lectures (60 minutes, including 15 minutes for lively discussion), 14 invited lectures (25 minutes, including 5 minutes for discussion), 24 oral communications (6 minutes, including one minute for discussion, spread among the sessions according to topic), and 79 poster communications (authors were near the poster at predetermined times for lively discussion) over the three days of the conference, which encompassed five sessions, including a "young session" for the young section of SPLC-CRS.

The conference featured excellent contributions from the invited plenary speakers. Clockwise from upper left: Ángel V. Delgado (University of Granada, Spain), João Nuno Moreira (University of Coimbra, Portugal), María Begoña Delgado Charro (University of Bath, United Kingdom), and Ruth Schmid (SINTEF Materials and Chemistry, Norway).

The first day started with a plenary lecture by Ángel V. Delgado (University of Granada, Spain), who provided a deep analysis of

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biomedical applications of magnetic nanoparticles, at present and in the perceived future. In his talk, he first focused on the versatility of magnetic particle preparation, concerning geometry and composition, and showed that the collection of available particles is magnified when the possible coatings are studied. He further gave an overview of existing information about the toxicity of these nanovehicles, including to what extent such potential toxic effects discourage the responsible authorities from approving the use of more than just a few designs. To end the day, and thanks to the generosity of the Faculty of Pharmacy of the University of Granada, this session featured the 2013–2015 SPLC-CRS Ph.D. Thesis Award. Ana del Moral García and María Adolfina Ruiz Martínez honored the winner, who was selected after a carefully independent review process. Edorta Santos Vizcaíno (University of the Basque Country, Spain) obtained this award with his thesis "Optimization of Cell Microencapsulation in Terms of Biosafety, Biomimesis and Applicability in Therapeutic Targets of Central Nervous System." The prize consisted of a certificate and the registration fee for the 43rd CRS Annual Meeting & Exposition (July 2016, Seattle, Washington, U.S.A.). A talk by Santos Vizcaíno presenting his Ph.D. research closed the session. The day concluded with a guided tour of Granada, where attendees enjoyed the old part of the city and discovered some curiosities of this Andalusian city, along with a welcome drink at the Hotel AC Palacio de Santa Paula, located in a charming old convent building.

The second day began with the plenary lecture by João Nuno Moreira (University of Coimbra, Portugal), which gave an insightful vision on nanotechnology-based strategies for cancer treatment, approaching them from a tumor biology-driven perspective. Session I (Discovery and Development of Nanomedicines) included the invited lectures of Juan Antonio Muñoz Orellana (University of Granada, Spain) on the protection of pharmaceutical inventions, Juan María Alfaro Sánchez (Neuron Bioservices, Spain) on the zebrafish's capacities to help biotech and pharmaceutical companies in the discovery and development of new drugs and nanodrugs, and Francisco Javier de la Mata (Ambiox Biotech, Spain) on carbosilane dendritic systems as a synthetic platform for the development of nanomedicines. Short talks selected from the abstracts closed this first session.

After a coffee break (poster viewing time with refreshments), session II, which was entirely organized by the young members of SPLC-CRS, featured the invited lecture of María José Alonso Fernández (University of Santiago de Compostela, Spain) on her view of current CRS activities, trying to open a discussion about the way meeting attendees might be willing to contribute to CRS and SPLC-CRS. She also summarized how CRS has influenced her scientific activity, her ultimate goal being to persuade mainly young scientists to be active in the communication and networking possibilities that both CRS and SPLC-CRS offer to them.

Active discussion took place during poster viewing.

Invited lectures from Paulo Roque Lino (University of Lisbon, Portugal) on the multivariate development of chitosan nanoparticles for the delivery of complex therapeutic human enzymes and María Carmen Leiva Arrabal (University of Granada, Spain) on experimental and clinical assays done during nanomedicine development against cancer were also included in the session. A round of short talks selected from Ph.D. student abstracts closed the session.

After lunch, the plenary lecture by Ruth Schmid (SINTEF Materials and Chemistry, Norway) focused on ultrasound-enhanced drug delivery using nanoparticle-stabilized microbubbles. She emphasized that the use of multifunctional nanoplatforms based on gas-filled microbubbles along with focused ultrasound can enhance drug delivery through biological barriers both into tumors and into the brain. Session III (New Strategies in the Treatment of Cancer and Infectious Diseases) started with an invited lecture by Ángel Montero Carcaboso (Hospital Sant Joan de Déu Barcelona, Spain). He discussed how nanotechnology can take advantage of unique genetic or biomarker alterations to enable active drug targeting to specific pediatric tumor cells. Next, the invited lecture by Jacob Lorenzo Morales (University of La Laguna, Spain) was devoted to the deep description of the combination of chemical therapies and gene silencing for the development of novel *Acanthamoeba* treatments. The session also included short talks selected from the abstracts.

The day ended with the SPLC-CRS General Assembly summarizing the current and prospective state of the local chapter, in which also the new directive board was elected, and with the traditional conference dinner at La Chumbera, including a fantastic flamenco show.

The last day of the conference started with a plenary lecture by María Begoña Delgado Charro (University of Bath, Great Britain) concerning recent advances on topical, transdermal, and nail drug delivery. She stressed the idea that transdermal and topical drug

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delivery remain active research and development areas. Session IV (Advanced Nanotechnologies in Biomedicine) consisted of three invited lectures by María Concepción Tros de Ilarduya Apaolaza (University of Navarra, Spain), Carmen Isabel Álvarez Lorenzo (University of Santiago de Compostela, Spain), and Bruno Sarmento (University of Porto, Portugal) on targeted nonviral vectors for gene delivery, medical devices as drug delivery platforms, and nanomedicines for modulating diabetes, respectively. An active discussion on clinical translation ensued as a consequence of these three remarkable invited lectures.

Time for oral communications preceded the beginning of session V (Advanced Nanoplatforms in the Management of the Disease). Invited lectures by María Luisa González Rodríguez (University of Seville, Spain) and Mazen M. El-Hammadi (Damascus University, Syria) were included in this session. Briefly, the first lecture was devoted to the analysis of recent advances and opportunities of nanocarriers in the inflammatory process, and the second invited lecture addressed the advances and prospects of nanosystems in medical imaging.

During the concluding remarks, María Adolfina Ruiz Martínez emphasized the success of the conference and thanked all the sponsors, contributors, and attendees. Finally, the best oral and poster presentation awards were given to Sandra Cristina Campos de Jesus (University of Coimbra, Portugal) and Juan José Arroyo Crespo (Centro de Investigación Príncipe Felipe, Valencia, Spain), respectively. Sandra and Juan José each received a certificate and a €100 cheque. Here are their presentation titles and coauthors:

PCL/Chitosan Nanoparticle Adjuvant Ability for HBsAg Vaccines
Sandra Jesus, Edna Soares, and Olga Borges

Polyglutamate-Based Combination Therapy in the Treatment of Advanced Breast Cancer
Juan J. Arroyo, Coralie Deladriere, Esther Masia, Vicent J. Nebot, Alison Paul, Ana Armiñán, and María J. Vicent

More details on the 11th Spanish-Portuguese Conference on Controlled Drug Delivery can be found in the abstract book available on the SPLC-CRS website (www.splc-crs.org/index.htm) under the 2016 meeting link. ■

Drug Delivery and Translational Research Update

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

Vinod Labhasetwar

2015 *DDTR* Outstanding Research Paper Award Winner

The Selection Committee and CRS are pleased to announce the following paper published in *DDTR* during 2015 for the award. Criteria such as translational nature of the research, overall impact, innovation, and significance of the study were considered in the selection process. The award is jointly sponsored by Springer-Nature and CRS. The corresponding author will be recognized at the 43rd CRS Annual Meeting & Exposition hosted in Seattle, Washington, U.S.A., July 17–20, 2016. Please join us in congratulating the authors of the paper for their outstanding achievement.

Engineered VEGF-Releasing PEG–MAL Hydrogel for Pancreatic Islet Vascularization
Edward A. Phelps, Kellie L. Templeman, Peter M. Thulé, and Andrés J. García
Drug Deliv. Transl. Res. 5:125-136 (2015)

In this paper, the authors have engineered biofunctionalized polyethylene glycol maleimide (PEG–MAL) hydrogels as a platform to deliver pancreatic islets to the small bowel mesentery and promote graft vascularization. The successful translation of the proposed approach could provide treatment for patients with type 1 diabetes mellitus.

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About the Corresponding Author

Andrés J. García is the Rae S. and Frank H. Neely Endowed Chair and Regents' Professor in the Woodruff School of Mechanical Engineering and the Petit Institute for Bioengineering and Bioscience at the Georgia Institute of Technology, U.S.A. He earned a B.S. in mechanical engineering with honors from Cornell University in 1991 and M.S.E. (1992) and Ph.D. (1996) degrees in bioengineering from the University of Pennsylvania. He completed a postdoctoral fellowship in cell and molecular biology at the School of Medicine of the University of Pennsylvania and then joined the faculty at Georgia Tech in 1998. Dr. García's research program integrates innovative engineering, materials science, and cell biology concepts and technologies to create cell-instructive biomaterials for regenerative medicine and generate new knowledge in mechanobiology. This cross-disciplinary effort has resulted in new biomaterial platforms that elicit targeted cellular responses and tissue repair in various biomedical applications, innovative technologies to study and exploit cell adhesive interactions, and new mechanistic insights into the interplay of mechanics and cell biology. Dr. García is recognized as an international leader in bioengineering, as demonstrated by his prestigious scholarly publications, invited presentations at conferences and research programs around the world, research funding from NIH, NSF, and private foundations, and membership on the editorial boards of leading biomaterial and regenerative medicine journals. In addition, his research has generated intellectual property and licensing agreements with start-up and multinational companies, demonstrating the translational potential and impact of this work. He has received several distinctions, including the NSF CAREER Award, Arthritis Investigator Award, Young Investigator Award from the Society for Biomaterials, Georgia Tech's Outstanding Interdisciplinary Activities Award, and the Clemson Award for Basic Science from the Society for Biomaterials. He has been recognized as a top Latino educator by the Society of Hispanic Professional Engineers. He is an elected Fellow of Biomaterials Science and Engineering (by the International Union of Societies of Biomaterials Science and Engineering), Fellow of the American Association for the Advancement of Science, Fellow of the American Society of Mechanical Engineers, and Fellow of the American Institute for Medical and Biological Engineering.

Join the leading scientists who are publishing their work in *DDTR* and compete for the 2016 *DDTR* outstanding research/clinical 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 the award criteria (controlledreleasesociety.org/about/Awards/Pages/DDTROustandingPaper.aspx).

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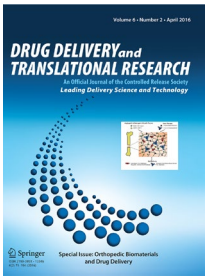

Orthopedic Biomaterials and Drug Delivery

DDTR volume 6, issue 2 is a special issue on orthopedic biomaterials and drug delivery. This elegantly developed issue has assembled leaders in nanomedicine, tissue engineering, and drug delivery, covering topics such as vascularization strategies, cell-based therapies and stem cell recruitment, novel drug delivery systems, and next-generation biomaterials for the regeneration of musculoskeletal tissues. Guest editors are Blanka Sharma and Shyni Varghese.

Blanka Sharma is an assistant professor of biomedical engineering at the University of Florida, U.S.A. Her research focuses on the development of biomaterials for regenerative medicine and targeted drug therapies, primarily in orthopedic applications. She received her undergraduate degree in chemical engineering from the University of Waterloo (Waterloo, Ontario, Canada), her Ph.D. from Johns Hopkins University (Baltimore, MD, U.S.A.) in the Department of Biomedical Engineering, and her postdoctoral training at the Cleveland Clinic (Cleveland, OH). Dr. Sharma served as director of research for Cartilix Inc., a start-up company based on her doctoral research, from 2005 to 2009, where she worked toward clinical translation of a hydrogel technology for cartilage repair in the knee. In 2014, she was featured by the American Society for Engineering Education as one of "20 Under 40" outstanding junior faculty in the country. She was also selected for the U.S. Bone and Joint Initiative Young Investigator Program and awarded a National Academies Kecks Futures Initiative grant.

Shyni Varghese is an associate professor of bioengineering and faculty director of the Bioinspired Materials and Stem Cell Engineering Laboratory at the University of California, San Diego, U.S.A. Her research focuses at the interface of biologically inspired materials and stem cells. She has coauthored over 80 peer-reviewed research articles, covering a wide range of interdisciplinary topics in stem cells, biomaterials, biologically inspired systems, and regenerative medicine. Her research activities have also resulted in over 12 patent disclosures. Examples of ongoing research activities in her laboratory involve developing functional biomaterials such as self-healing materials, technologies to improve stem cell based therapies including activating endogenous stem cells, engineered functional tissue grafts, and organ-on-a-chip systems. She is on the editorial boards of a number of journals and a consultant to various biotech and device companies. ■

Patent Watch

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

This article briefly summarizes novel aspects of selected United States (U.S.) patents involving controlled release or delivery that were issued from July 1 to December 31, 2015. Greater detail on each can be found on the U.S. patent website at http://patft.uspto.gov/.

U.S. patent 9,221,893 – Preparation and use of hyaluronic acid-protein conjugates for controlled delivery of treatment to the liver and past the liver are disclosed.

U.S. patent 9,220,689 – Nano-sized cationic acrylic copolymer particles are used as templates for deposition of a silica shell to create core-shell nanoparticles for controlled delivery of payload in response to pH.

U.S. patent 9,216,198 – Electrospun fibers containing nitric oxide releasing materials or particles are described for controlled release of nitric oxide.

U.S. patent 9,212,259 – Polymers that are liquid at room temperature and gel at physiological pH/temperature are used for controlled release of nitric oxide from implants.

U.S. patent 9,089,830 – Incorporation of a volatile burst aid into interfacially polymerized microcapsules enables temperature triggered burst release in relation to the vapor pressure of the volatile component.

U.S. patent 9,212,335 – A mixture of a diamine and perfuming aldehydes and/or ketones in the presence of water provides an extended release profile for the perfuming ingredients.

U.S. patents 9,198,877 and 9,205,062 – Multiple adhesive layers with varying drug release properties are used to control drug delivery through the skin.

U.S. patent 9,205,051 – Porous sustained release silicon implants with drug fully dispersed throughout the structures are disclosed.

U.S. patent 9,199,035 – Electrochemically driven pumps that employ an electrochemically active gas to displace and deliver fixed amounts of drug at appropriate times to locations such as the eye are disclosed.

U.S. patent 9,132,231 – A wearable chambered controlled drug delivery device consisting of a gas generator to incrementally deliver drug is described.

U.S. patent 9,204,632 – Controlled release microcapsules of pesticides, herbicides, and the like are produced by *in situ* polymerization of a polyurethane shell.

U.S. patent 9,156,745 – Robust controlled release fertilizers consisting of a fertilizer core and a polyurethane coating with an organic carbonate additive are described.

U.S. patent 9,120,709 – Polymer layering is used to create a controlled release urea fertilizer.

U.S. patent 9,198,875 – A polymeric cyclodextrin host is used in layered decomposable polyelectrolyte films for controlled release of hydrophobic bioactive materials.

U.S. patent 9,186,640 – Coacervates consisting of a lipophilic core such as fish oil and shell formed from cationic and anionic polymers are described.

U.S. patent 9,155,703 – This invention involves the formation of a molecular bond to alter the structural integrity of a polymeric network and control release of active agents.

U.S. patents 9,114,176 and 9,095,623 – Drug is incorporated in a conjugate framework with affinity ligands and multivalent cross-linking agents that bind with exogenous target molecules. Competition between the exogenous target molecules and affinity ligands for binding with the cross-linking agents triggers release of the drug.

Patent Watch continued

U.S. patent 9,198,840 – An encapsulated evaporative cooling agent is applied over color cosmetics to control the rate of water/volatile component loss and extend the functional time of the cosmetic.

U.S. patent 9,149,426 – Biocompatible, biodegradable nanoparticle systems composed of drug and poly(ortho ester) polymers for zero order delivery are disclosed.

U.S. patent 9,186,351 – A dosage form consisting of a pH lowering agent and a gel-forming polymer creates a pH stable environment to extend melatonin release into the intestinal region.

U.S. patent 9,173,949 – High-molecular-weight dendritic polymers with biodegradable spacers are employed for targeted drug delivery to tumors.

U.S. patents 9,155,311 and 9,078,445 – Aluminum phosphate containing bioactive molecules are dispersed within a polymer to control antimicrobial resistance upon exposure to water.

U.S. patent 9,138,417 – Interfacial polymerization of a vinyl monomer is used to create controlled release particles of an antibiotic.

U.S. patent 9,125,807 – *In situ* formation of a hydrogel is used for controlled delivery of a therapeutic agent to the eye.

U.S. patent 9,114,187 – A printable identification wristband with a controlled release antimicrobial coating is disclosed.

U.S. patent 9,119,793 – Floatable, swellable, and bioadhesive gastroretentive formulations of doxycycline are described for maximum therapeutic efficacy of doxycycline.

U.S. patent 9,119,780 – An ester of a functional active is used for controlled delivery of the active by hydrolysis. ■

Companies in the News

Compiled by Steven Giannos, Independent Consultant

March

Ironwood Pharmaceuticals Initiates Phase IIb Clinical Trial of IW-3718 in Refractory Gastroesophageal Reflux Disease

Business Wire: March 23, 2016 – CAMBRIDGE, MA, U.S.A. – Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) today announced that it initiated a phase IIb clinical trial of IW-3718 in patients with refractory gastroesophageal reflux disease (GERD). Refractory GERD is a chronic condition in which patients continue to suffer from symptoms such as heartburn and regurgitation despite receiving treatment with a proton pump inhibitor (PPI). Data from this trial are expected in 2017.

"There is a significant unmet medical need among the estimated 10 million patients in the United States with refractory GERD," said Mark Currie, Ph.D., chief scientific officer and president of research and development at Ironwood. "For these patients, PPIs are not enough to control their heartburn and regurgitation. They continue to suffer from frequent and bothersome symptoms, and there is a dearth of approved prescription medicines for this condition. For these reasons, the advancement of IW-3718 is a top priority for Ironwood."

The randomized, double-blind, placebo-controlled, dose-ranging phase IIb clinical trial is designed to evaluate the safety, efficacy, and dose-response relationship of IW-3718. The trial is expected to enroll approximately 260 adult patients who have been diagnosed with GERD and report experiencing heartburn or regurgitation at least four days per week during the previous eight weeks despite ongoing PPI treatment. The study design calls for eligible patients to continue taking their daily PPI therapy and to be randomized to receive additional treatment with placebo or one of three doses of IW-3718, twice-daily for eight weeks. The primary efficacy endpoint is change from baseline in heartburn severity.

Ironwood previously reported positive data from its randomized, double-blind, placebo-controlled phase IIa study of IW-3718 for refractory GERD. Data from that study showed that IW-3718 improved heartburn severity in the intent-to-treat population. IW-3718 was generally well-tolerated with the most common adverse event being constipation.

An estimated 45 million Americans have gastroesophageal reflux disease (GERD), an estimated 10 million of whom are thought to suffer from the refractory form of the condition, meaning they continue to experience symptoms such as heartburn and regurgitation despite receiving the current standard of care treatment with a proton pump inhibitor (PPI). While PPIs suppress production of stomach acid, research suggests reflux of bile from the intestine into the stomach and esophagus may play a role in the ongoing symptoms of refractory GERD. There are few FDA-approved treatment options for these patients. If left untreated, refractory GERD can lead to serious complications including Barrett's esophagus and, in rare instances, esophageal cancer.

IW-3718 is a novel, investigational gastric retentive formulation of a bile acid sequestrant, developed by Ironwood using the proprietary Acuform® drug delivery technology licensed from Depomed, Inc. IW-3718 is designed to remain in the stomach and duodenum (upper small intestine) over an extended period of time and to work in combination with a PPI to reduce the detrimental effects of bile and acid on the esophagus.

Cerulean Announces Publication Showing CRLX101 Localizes Selectively in Human Tumors, Sparing Adjacent Healthy Tissue

Business Wire: March 23, 2016 – WALTHAM, MA, U.S.A. – Cerulean Pharma Inc. (NASDAQ:CERU), a clinical-stage company developing nanoparticle-drug conjugates (NDCs), today announced the publication of clinical data for its lead compound, CRLX101, in the journal *Proceedings of the National Academy of Sciences* (*PNAS*). The publication highlights results from an investigator-sponsored clinical trial, in which pre- and post- treatment tumor biopsies from patients with gastric cancer treated with CRLX101 show the presence of CRLX101 and its payload, camptothecin, in tumors, and their absence in surrounding normal tissue. Importantly, inhibition of the molecular targets of CRLX101 was demonstrated in post-treatment biopsies. The article was published online. Initial results from the trial were presented at the 2015 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics on November 7, 2015.

"CRLX101 delivers a powerful anti-cancer drug to the tumor, sparing adjacent healthy tissue, results that directly translate observations from the lab to the clinic," stated Mark Davis, Ph.D., Warren and Katharine Schlinger Professor of Chemical

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Engineering at California Institute of Technology. "Toxicities prevented the clinical development of camptothecin. Creating an NDC that incorporates camptothecin as its payload overcomes this major hurdle."

"The data Dr. Davis and colleagues at the City of Hope Comprehensive Cancer Center published in *PNAS* demonstrate the power of NDCs," said Christopher D.T. Guiffre, president and chief executive officer of Cerulean. "Dynamic tumor targeting is no longer something we have shown only in rodents—it has now been confirmed in humans with CRLX101. Targeting tumors and sparing healthy tissue has long been a major objective of oncology drug development, and CRLX101 achieves that important goal."

The article describes results from nine patients with advanced gastric cancer enrolled in a pilot study sponsored by the City of Hope Comprehensive Cancer Center. All patients progressed on at least one prior line of systemic therapy. Tumor and adjacent healthy tissue biopsies were obtained through endoscopic-assisted biopsies prior to and 24–48 hours after receiving 15 mg/m^2 of CRLX101. In all nine patients, the CRLX101 payload, camptothecin, was detected in patient tumor tissue and neither CRLX101 nor camptothecin was detected in post-treatment healthy tissue samples adjacent to tumors. Immunohistochemistry in patient tumors demonstrated that sufficient camptothecin is released from CRLX101 in the post-treatment tumors to have the intended biological effects of inhibiting its molecular targets, topoisomerase-1 and hypoxia inducible factor 1α, two proteins that are believed to be involved in the progression of the cancer.

STENTYS Announces the CE Marking of the Self-Apposing Stent for Left Main Coronary Artery Disease

Business Wire: March 21, 2016 – PRINCETON, NJ, U.S.A. and PARIS, France – STENTYS (FR0010949404 — STNT) (Paris: STNT), a medical technology company commercializing the world's first and only Self-Apposing® coronary stent, today announced that Xposition S, the Sirolimus-Eluting Self-Apposing Stent, received CE marking for the treatment of unprotected left main coronary artery disease on the basis of the results from a study published last year in the peer-reviewed journal *Catheterization and Cardiovascular Interventions*.

When treating patients with left main coronary artery disease, the large diameter of the left main artery and the significant vessel tapering at that location represents serious challenges for conventional balloon-expandable DES that often result in important stent structural deformations. The STENTYS Self-Apposing Stent can adapt to vessels with varying diameters and ensure optimal fit to the vessel wall along the entire stented length. Xposition S new delivery catheter also enables very accurate stent positioning, a key feature when the lesion is close to the aorta.

The single center, retrospective, two-arm, controlled study, conducted by Carlo Briguori, M.D., Ph.D. (Clinica Mediterranea, Italy), included 75 consecutive patients with tapered distal unprotected left main coronary artery lesions treated with STENTYS DES. The authors concluded that the STENTYS stent offers a valid treatment alternative for this indication.

Gonzague Issenmann, cofounder and chief executive officer of STENTYS, commented: "This CE marking confirms the adequacy of our technology in this complex setting and now allows us to quickly start the multicentric study that will evaluate the efficacy of Xposition S in 200 patients in this indication."

STENTYS is developing and commercializing innovative solutions for the treatment of patients with complex artery disease. STENTYS' Self-Apposing® drug-eluting stents are designed to adapt to vessels with ambiguous or fluctuating diameters in order to prevent the malapposition problems associated with conventional stents. The APPOSITION clinical trials in the treatment of acute myocardial infarction showed a very low one-year mortality rate and a faster arterial healing compared to conventional stents. The company's product portfolio also includes MiStent SES®, a coronary DES whose new drug delivery mechanism is designed to match vessel response, and is marketed through STENTYS' commercial network in Europe, the Middle East, Asia, and Latin America.

Juniper Pharmaceuticals Affirms Development Pathway for Oxybutynin Intravaginal Ring for Overactive Bladder in Women

PRNewswire: March 21, 2016 – BOSTON, MA, U.S.A. – Juniper Pharmaceuticals, Inc. (NASDAQ: JNP) ("Juniper" or the "company"), a women's health therapeutics company, today confirmed that it met with representatives of the Food and Drug Administration (FDA) in a Pre-IND meeting concerning JNP-0101, its oxybutynin intravaginal ring (IVR) for the treatment of overactive bladder (OAB) in women.

"It was a very collaborative meeting," commented Dr. Bridget Martell, chief medical officer. "The regulatory path for JNP-0101 is clear, and we are on track to complete our IND-enabling preclinical work for this promising product candidate and file our IND application later this year. We plan to begin a phase 2a bioavailability and dose finding clinical study once the IND is active."

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Overactive bladder is characterized by involuntary contraction of the detrusor muscles before the bladder is full. This chronic urological condition affects an estimated 20 million women in the United States, with approximately nine million receiving pharmacologic therapy. The domestic market for OAB therapeutics was $1.3 billion in 2014.

Oxybutynin addresses OAB by decreasing muscle spasms of the bladder and the frequent urge to urinate caused by these spasms. While the most common prescription drug is generic oral oxybutynin, approximately half of women treated discontinue its use within the first year due to undesirable side effects. Juniper believes that delivering oxybutynin intravaginally using its IVR technology could provide an effective treatment for the condition while improving systemic side effects.

It is expected that JNP-0101 will utilize the shared vascular and lymphatic networks of the vagina and bladder to achieve localized absorption of oxybutynin by relevant tissues in higher concentrations, while bypassing hepatic first pass metabolism. Metabolism in the liver can result in increased active metabolites, which are purported to contribute the majority of experienced side effects.

The sustained-delivery oxybutynin IVR is also expected to improve compliance, as well as increase convenience for many patients and improve disease management and overall health outcomes.

Juniper plans to utilize the 505(b)(2) regulatory pathway in the United States. Requisite clinical trials under this pathway would include a phase 2a bioavailability and dose finding study followed by a pivotal phase 3 clinical trial.

Juniper Pharmaceuticals, Inc., is focused on developing therapeutics that address unmet medical needs in women's health. The company is advancing a pipeline of proprietary product candidates that leverage novel intravaginal drug delivery technologies. Juniper's commercial product, CRINONE® 8% (progesterone gel), is marketed by Merck KGaA, Darmstadt, Germany, in over 90 countries worldwide and by Allergan, Inc., in the United States. Please visit www.juniperpharma.com for more information.

Gecko Biomedical Raises €22.5 Million Led by Sofinnova Partners

Business Wire: March 17, 2016 – PARIS, France – Gecko Biomedical ("Gecko"), a medical device company developing innovative polymers to support tissue healing, has closed a €22.5 million financing round. This series A2 round was led by Sofinnova Partners, which becomes the largest investor in Gecko, with support from Bpifrance and existing series A investors Omnes Capital, CM-CIC Innovation, and CapDecisif Management, who invested in the company in December 2013. In conjunction with the financing, Antoine Papiernik at Sofinnova Partners and Chahra Louafi at Bpifrance have joined Gecko's board of directors.

Gecko was co-founded by Christophe Bancel and Bernard Gilly (both from the iBionext Network), Prof. Jeff Karp (Harvard Medical School, Brigham and Women's Hospital – Boston, MA, U.S.A.), and Prof. Bob Langer (Massachusetts Institute of Technology – Cambridge, MA, U.S.A.) in late 2013 to advance a state-of-the-art polymer platform. One of its lead inventors, Dr. Maria Pereira, was named a Forbes 2015 "30 under 30." Pereira is Gecko's head of research.

The funds raised will be used to further advance the development of Gecko's first platform, GB-02, for cardiovascular reconstruction and beyond. In addition, the funds will be used to leverage its fully industrialized platform in novel areas including guided tissue repair and localized drug delivery.

Gecko's platform has demonstrated its ability to be fully industrialized, with a unique level of biocompatibility and a great potential in terms of versatility.

This platform is based on proprietary polymers with unique chemical and physical properties, including high viscosity, hydrophobicity, and fast "on demand" curing for precise local delivery and *in situ* adhesion. Upon curing, an elastic biodegradable film is formed. The structure of the polymer is tunable, allowing customization for various applications and tissues.

Christophe Bancel, Gecko's CEO, commented: "Our investors' support will enable us to complete our international clinical plans in cardiovascular surgery, which, if positive, will allow us to seek our first regulatory approval within one year. In addition, the funds will be used to expand our GB-02 platform to additional applications in tissue reconstruction. We will also drive the development of our next-generation polymer GB-04, for sutureless closure."

Antoine Papiernik, managing partner at Sofinnova Partners, added: "We are thrilled to be involved with Gecko Biomedical, a company which combines all the key features we are looking for when investing in a company: a very strong management team and a world-class platform technology with a multitude of possible paradigm-shifting applications."

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Gecko Biomedical is a privately owned medical device company based in Paris, France, that is dedicated to the rapid development and commercialization of a unique biopolymers platform. Gecko's first product (GB-02) is an innovative polymer for tissue healing, targeting cardiovascular reconstruction as an initial indication. The structure of GB-02 is tunable, allowing customization for various applications and tissues. Gecko's biopolymers platform is fully industrialized and highly versatile, with potential novel applications in other fields of tissue reconstruction, such as guided tissue repair and localized drug delivery.

Gecko's platform is based on proprietary biopolymers with unique chemical and physical properties, including high viscosity, hydrophobicity, and fast "on demand" curing for precise local delivery and *in situ* adhesion. The company's technologies are derived from world-class research and intellectual property from the laboratories of Robert Langer (MIT) and Jeff Karp (Brigham and Women's Hospital), who cofounded the company in 2013, alongside Christophe Bancel and Bernard Gilly from the iBionext Network. For more information, please visit www.geckobiomedical.com.

Adama Licenses Starpharma's Priostar® Dendrimer Technology for the Development and Commercialization of a Novel 2,4-D Product for the U.S. Market

PRNewswire: March 17, 2016 – MELBOURNE, Australia, and TEL-AVIV, Israel – Starpharma (ASX: SPL; OTCQX: SPHRY) and Adama today announced the licensing by Adama of Starpharma's Priostar® dendrimer technology for the development and commercialization of an enhanced, proprietary 2,4-D herbicide for the U.S. market. 2,4-D is one of the top three herbicides sold worldwide, with global sales in 2014 estimated by Phillips McDougall to be around US$680 million. The U.S. market in 2014 was worth approximately US$115 million, and it has been projected by the U.S. Department of Agriculture to grow by more than 70% by 2020.

Adama has already commenced development of a novel and unique 2,4-D product containing the Priostar® dendrimer technology, which is expected to provide better flexibility and weed control benefits to the grower, as well as improved safety. This will allow for on-target application, thus benefiting the environment by reducing the amounts of product required.

Under the license, Starpharma will receive royalties on sales of the proprietary Adama Priostar®-improved 2,4-D products. In addition to the United States, the agreement also includes a mechanism to expand the license into additional territories.

Sami Shabtai, head of innovative development at Adama, commented, "As a farmer-centric company, Adama constantly strives to bring new and innovative solutions to farmers that will simplify their lives. The innovative nature and superior performance of the Priostar® formulations fit well with our strategy to deliver simple and efficient solutions to farmers to help them grow. This is yet another step in the evolution and differentiation of our offering, as we continue to introduce unique mixtures and formulations to the market."

Dr. Jackie Fairley, CEO of Starpharma, said, "We enjoy a positive relationship with Adama, and their extensive trials of Priostar®-improved 2,4-D formulations have led to this license agreement. With Adama's strong, proven record of innovative product development, we are very pleased to have them as commercial partners for Priostar®-improved 2,4-D products. In addition, we continue to explore other Priostar® product opportunities with Adama."

Starpharma's Priostar® dendrimer technology offers formulation and efficacy benefits in crop protection applications including:

- Improved efficacy;
- More concentrated formulations to reduce transport costs;
- Reduction in solvent requirements; and
- Increased adhesion, to reduce losses due to rain run-off, and the need for multiple applications.

Adama is one of the world's leading crop protection companies. We strive to Create Simplicity in Agriculture—offering farmers effective and efficient products and services that simplify their lives and help them grow. With one of the most comprehensive and diversified portfolios of differentiated, high-quality products, Adama's 4,900 people reach farmers in over 100 countries across the globe, providing them with solutions to control weeds, insects and disease and improve their yields. For more information, visit us at www.adama.com and follow us on Twitter at @AdamaAgri.

Starpharma Holdings Limited, an Australian ASX 300 company, is a world leader in the development of novel products based on dendrimers, a type of synthetic nanoscale polymer that is highly regular in size and structure, for pharmaceutical, life science, and other applications. Starpharma has three core development programs: VivaGel® portfolio, DEP™ drug delivery, and agrochemicals with a number of products being developed internally and externally via commercial partnerships. Partners include AstraZeneca, Ansell, and Okamoto, as well as other named and undisclosed partnerships with leading global companies in pharmaceuticals and agrochemicals. For more information, please visit www.starpharma.com.

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Chrono Therapeutics' Smoking Cessation Technology Demonstrates Significant Reduction in Nicotine Cravings

PRNewswire: March 4, 2016 – CHICAGO, IL, U.S.A. – Chrono Therapeutics, a pioneer in digital drug therapy, today announced that clinical data for the company's smoking cessation technology showed a statistically significant reduction in nicotine cravings in a trial of adult male smokers. The data were presented today at the Society for Research on Nicotine and Tobacco's 22nd Annual Meeting.

Chrono's wearable transdermal drug delivery device times nicotine delivery to when smokers have their strongest cravings. For example, 75% of all smokers reach for their first cigarette within 30 minutes of waking up. The Chrono solution is designed to deliver the first dose of nicotine replacement therapy (NRT) shortly before a smoker wakes up and then creates a pattern of "peaks and troughs" of nicotine delivery throughout the rest of the day to assure the smoker has more nicotine support when cravings are predicted to be strongest.

"In the United States, 70% of smokers want to quit, but quitting is extremely difficult. In fact, most people try 8–10 times, and this includes quit attempts with standard cessation medications like nicotine patch and gum and prescription drugs like varenicline," said Alan Levy, Ph.D., chairman and CEO of Chrono Therapeutics. "Gums and patches are designed to help manage cravings, but they are only 5–9% effective. Our goal is to solve this crisis of public health with an innovative, integrated smoking cessation solution, and the data we presented demonstrates that we are on the right path."

The clinical trial was a randomized, double blinded study of 24 adult males who smoked 11 or more cigarettes per day, indicating a high level of nicotine dependence. The subjects were divided into two groups. Test group subjects had nicotine administered over a 30-hour time period via Chrono's prototype device that delivered nicotine according to Chrono's "peaks and troughs" profile. Control subjects had a placebo solution, with no nicotine, administered at the same intervals via the same prototype device. Across both groups, subjects showed no serious adverse events or study withdrawals due to an adverse event. Skin irritation assessment showed no signs of irritation or erythema.

Cravings were assessed via three different methods: the Questionnaire for Smoking Urges (QSU), the Mood and Physical Symptoms Scale (MPSS), and a single craving question, each of which is a validated tool to assess cravings. When compared to subjects treated with placebo, test subjects had a statistically significant and clinically meaningful reduction in cravings for all assessment methods (p = 0.035; p = 0.034; and p = 0.016, respectively).

"Achieving statistical significance in a 24-subject trial is very striking and happens infrequently in biopharma; so these results are very encouraging," noted Wende Hutton, general partner at Canaan Partners and a member of Chrono's board of directors. "Quitting smoking is one of the simplest ways to improve global public health, but as the dismal efficacy of current therapies demonstrates, it is also one of the hardest. I'm very excited to be working with a company that has the potential to solve such a serious problem."

Effective care of the most hard-to-treat conditions requires approaches beyond simply taking medicine. Chrono's team is developing the first wearable transdermal drug delivery device that optimizes drug dosing, is embedded with sensor technology to track usage, and is connected via Bluetooth to an evidence-based smartphone application that delivers real-time personalized behavioral support to keep users on track to achieve their goals. Chrono's first application is in smoking cessation, enabling smokers to overcome the world's deadliest addiction. For more information, visit www.chronothera.com.

Gensco Laboratories Launches the First Transdermal Medication for Acute Gout Flares

PRNewswire: March 2, 2016 – MIAMI, FL, U.S.A. – Gensco Laboratories announces ColciGel™, a new transdermal medication indicated for the treatment of acute gout flares in adults.

Gout, an extremely painful form of inflammatory arthritis, affects more than 4% of Americans and about 10% of men over the age of 60. It is more common in women after menopause. The disease occurs due to an excess of the bodily waste, uric acid. The acid is deposited as needle-like crystals in the joints or in soft tissue. These crystals cause redness, swelling, stiffness, and intense pain in the joints, which in turn can create gout flares.

"Unfortunately, gout attacks often occur without warning. This sudden attack is referred to as a 'flare' and will normally subside within 3–10 days, but during that timeframe, the pain is excruciating if untreated," said Gary Myerson, M.D., founding fellow of the American College of Rheumatology. "The secret to the treatment of the acute gout attack is to be prepared and treat the flare early."

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A new transdermal gel has been developed and is now available by prescription only to treat the symptoms of gout attacks. "ColciGel™ is a transdermal medication that provides rapid relief of pain at the first sign of acute gout flares without gastrointestinal problems. The medication should be applied directly on the site of the pain," said Robert L. Wilbur, Pharm.D. C.Ph. "ColciGel™ offers gout sufferers, and physicians that treat these patients, an important new option to stay ahead of the horrible pain before it strikes."

Copay assistance and cash pay programs are available to all patients through participating specialty pharmacies. "As a pharmaceutical manufacturer, we have a responsibility to provide access to safe and effective medications. We recognize the need to assist with the financial burden as our duty," said Carlos Alfaras, CEO of Gensco Laboratories. "Our corporate focus is to utilize our resources on innovative research and the development of unique delivery systems, and it aligns with our specialty partner's efforts to improve access and the quality of life for patients who suffer from debilitating diseases. The Gensco specialty pharmacy distribution partnerships foster the growing need to focus on disease states which our new transdermal ColciGel™ serves."

ColciGel™ is offered through specialty pharmacies including but not limited to Apogee Bio-Pharm, Aureus Health Services, BriovaRx, Cardinal Health Specialty, Cigna Health, MagellanRx Pharmacy, ProCare Rx Pharmacy, Senderra Rx Pharmacy, SMP Pharmacy Solutions, and Walgreens Specialty Pharmacy.

Even though nine out of 10 gout sufferers say gout has affected their daily lives, one in five isn't doing anything at all to treat the disease—and only 10% of gout sufferers are getting needed treatment. If you are suffering from gout, learn more by speaking with your doctor or visiting www.gouteducation.org. For more information on ColciGel™, visit www.colcigel.com.

Gensco Laboratories is a specialty pharmaceutical company focusing on research, development, and marketing of transdermal prescription products. As an innovator of pharmaceutical products and the development of patented drug delivery systems, Gensco is dedicated to the continual pursuit of novel and effective therapies that improve health.

Johnson & Johnson Innovation Unveils JLABS @ TMC to Help Catalyze Early Stage Research Through to Commercialization for Healthcare Solutions in Houston

PRNewswire: March 2, 2016 – HOUSTON, TX, U.S.A. – Johnson & Johnson Innovation LLC today opened JLABS @ TMC, a new 34,000-square foot life sciences incubator providing entrepreneurs shared lab space, private offices, and modular laboratory suites, as well as state of the art equipment and value-added operational, education, and business services. The new JLABS facility can accommodate up to 50 startups, and will open with 21 companies that represent a range of disciplines and geographies. This first "class" of resident startups includes the four winners of the JLABS Quick Fire Challenge, which awards promising early stage innovation companies with residency at the facility.

JLABS @ TMC builds on the successful JLABS model and is the fifth JLABS facility to open in the United States. The Houston site is the first to open with a medical device prototype lab, including a 3D printer, which will provide entrepreneurs access to highly specialized tools, as well as skills building programs to design and develop smart health technologies.

JLABS @ TMC is housed within the TMC Innovation Institute, adjacent to TMC's life sciences accelerator TMCx, enhancing its think tank–like environment and encouraging sharing of ideas, collaboration among JLABS, TMC and TMCx residents, and facilitation of relationships with investors and venture capitalists.

"We're thrilled to expand our JLABS initiative into Houston," said Paul Stoffels, M.D., chief scientific officer and worldwide chairman, pharmaceuticals, Johnson & Johnson. "The city's rich research, academic, and investment communities provide a robust ecosystem of early stage innovation and present a unique opportunity to collaborate with Texas startups to deliver much-needed therapeutics, medical devices, and consumer health solutions to patients and consumers more quickly."

"We have been eagerly awaiting this day when JLABS @ TMC opens its doors and immediately enhances our already robust ecosystem of talented entrepreneurs who are solving the greatest unmet healthcare needs of our generation," said Robert C. Robbins, M.D., president and CEO of the Texas Medical Center. "TMC has spent decades making healthcare history, and now these business accelerators housed at TMC will take innovation to new heights."

JLABS @ TMC joins a network of facilities that are based throughout North America in life science clusters, including San Diego (flagship), San Francisco, South San Francisco, Boston and, opening this spring, the first international location in Toronto, Canada. These facilities are currently home to more than 100 early stage companies advancing bio/pharmaceutical, medical device, consumer, and digital health programs. The JLABS facilities will have a total capacity for 225 resident companies once all six are open and operational.

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"Houston is already a very active life sciences hub, and we've recently seen a drive to further embrace the industry, establish clear leadership in biotech innovation, and close the gap between research and commercialization," said Melinda Richter, head of JLABS. "JLABS is ideally suited to catalyze this result, not only through supporting the development of new healthcare solutions for patients but also by providing startups with access to the broader JLABS network and its family of incubators."

Texas Medical Center hosts an increasing number of life sciences and biotech companies via commercialization initiatives, such as its Innovation Institute, steadily growing the opportunities for academic and industry partnerships in Houston.

Johnson & Johnson Innovation has entered into a collaboration with PerkinElmer, Inc., to outfit the new JLABS @ TMC facility with world-class lab instruments and software as well as to provide training, OneSource® Laboratory Services, and on-site technical support for the resident companies.

All JLABS locations are accepting applications from biotech, pharmaceutical, medical device, consumer, and digital health companies. To apply, visit www.jnjinnovation.com/jlabs.

Nuvo Research® Inc. Completes Reorganization into Two Publicly Traded Companies

PRNewswire: March 1, 2016 – MISSISSAUGA, ON, Canada – Nuvo Pharmaceuticals Inc. (TSX: NRI) (Nuvo Pharma or the company), formerly known as Nuvo Research Inc. and Crescita Therapeutics Inc. (TSX: CTX) (Crescita), today announced the completion of the reorganization of Nuvo Research Inc. into two separate publicly traded companies (the reorganization). As a result of the reorganization, the shareholders of what was formerly Nuvo Research Inc. now own 100% of Nuvo Pharma, a revenue and EBITDA generating commercial healthcare company, and 100% of Crescita, a drug development company. The reorganization was approved by the shareholders of Nuvo Research Inc. at a special shareholders meeting on February 18, 2016, and by the Ontario Superior Court of Justice on February 24, 2016.

"This transaction gives both businesses greater flexibility to focus on, and pursue, their respective growth strategies," said John London, president and CEO of Nuvo Pharma. "Nuvo Pharma is a profitable business with significant revenue and EBITDA growth potential." "We are very excited about the launch of Crescita," added Dan Chicoine, Chairman and CEO of Crescita. "We have exciting technologies, a proven management team that has obtained FDA approval for four topical pharmaceutical products, and a strong balance sheet to support our growth."

Under the reorganization, existing Nuvo Research Inc. share certificates now represent common shares of Nuvo Pharma and the right to receive a share certificate representing an equal number of Crescita common shares. The distribution record date (the record date) for certificates representing Crescita common shares is Thursday March 3, 2016. However, the TSX has implemented due bill trading for the Nuvo Pharma common shares (TSX: NRI) until the close of trading on Friday March 4, 2016. Accordingly, shareholders who purchase Nuvo Pharma common shares through the facilities of the TSX prior to the close of trading on Friday March 4, 2016, will automatically receive one Crescita common share for each Nuvo Pharma common share purchased. Crescita common shares (TSX: CTX) are expected to commence trading on the TSX on Monday March 7, 2016. Nuvo Pharma and Crescita shareholders are encouraged to contact their brokers for additional information.

As part of the reorganization, Nuvo has changed its name from "Nuvo Research Inc." to "Nuvo Pharmaceuticals Inc." Effective with the reorganization, Nuvo Pharma (TSX: NRI) is a commercial healthcare company with a portfolio of commercial products and pharmaceutical manufacturing capabilities. Nuvo Pharma has three commercial products that are available in a number of countries: Pennsaid 2%, Pennsaid, and the heated lidocaine/tetracaine patch. Pennsaid 2% is sold in the United States by Horizon Pharma plc (NASDAQ: HZNP) and is available for partnering in certain other territories around the world. Nuvo Pharma manufactures Pennsaid for the global market and Pennsaid 2% for the U.S. market at its FDA licensed GMP facility in Varennes, Québec. For additional information, please visit www.nuvopharmaceuticals.com.

Effective with the reorganization, Crescita (TSX: CTX) is a well-capitalized biotech company that owns a pipeline of topical and transdermal product candidates for treating medical conditions in a number of therapeutic areas, including pain and dermatology. Crescita owns multiple proprietary drug delivery platforms that support the development of patented formulations that can facilitate the delivery of active drugs into or through the skin. Crescita has one commercial product, Pliaglis, that is licensed globally (except for Canada, the United States, and Mexico, where Crescita owns the rights). Crescita's board and management team have demonstrated success in building Nuvo Research Inc., including developing multiple drugs that are now approved and commercialized and negotiating multiple transactions that have generated more than $100 million in non-dilutive funding. For additional information, please visit www.crescitatherapeutics.com.

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Propeller Partners with Global Drug Delivery Systems Provider Aptar Pharma for Development of a Next-Generation, Integrated, Connected Metered Dose Inhaler

PRNewswire: February 25, 2016 – MADISON, WI, U.S.A. – Propeller Health, the leading digital health solution for respiratory medicine, today announced a partnership with Aptar Pharma (Aptar), a global drug delivery systems provider, including technology for metered dose inhalers systems (MDIs) for treatment of asthma and chronic obstructive pulmonary disease (COPD). Under the terms of the agreement, Propeller and Aptar will jointly develop the world's first integrated cMDI, with an integrated sensor and a novel electronic dose counter. The device is currently available for licensing and is expected to enter clinical studies later this year.

Pressurized MDIs are the most common type of inhaler device on the market today, with over 600 million units manufactured globally. They deliver aerosolized medications such as bronchodilators, corticosteroids, and combinations that are used daily by patients with chronic respiratory diseases such as asthma or COPD. The Propeller-Aptar partnership will create the first connected inhaler, the most significant improvement in MDIs since the industry added mechanical dose counters over ten years ago.

The new inhaler will combine Aptar MDI components and sensor technology with Propeller electronics directly into the inhaler housing, allowing for accurate and reliable monitoring of when each patient uses their inhaled medication. Information about the use of medications delivered by the cMDI will be put to work as part of the Propeller digital system for patients and providers. Leveraging existing apps, emails, text messages, and other feedback, patients are able to learn more about their disease, how to better manage it, and how to stay on track with their prescribed dosing instructions. In addition, physicians can identify individuals who need more help controlling symptoms, and care managers can efficiently focus on higher risk patients who need more personalized attention.

Propeller's platform is 510(k) cleared and compatible with a majority of MDIs on the market today including controller medications such as GSK's Flovent®, Merck's Dulera®, Teva's QVAR®, and others, as well as reliever medications such as GSK's Ventolin® HFA, Merck's Proventil® HFA, Teva's ProAir® HFA, and generic albuterol. It is also cleared and compatible with medications utilizing Boehringer Ingelheims's RESPIMAT® soft mist inhaler (SMI) and GSK's Diskus® dry powder inhaler (DPI).

"Patients and physicians deserve better designed inhalers that are easier to use and help them successfully treat their chronic respiratory disease," said David Van Sickle, CEO of Propeller. "We are excited to work with Aptar to bring important digital innovation to respiratory drug delivery. We expect our connected inhaler to become the cornerstone for a platform of digital programs that will support and encourage better management of and quality of life with chronic respiratory disease. Together I believe we have the scale and expertise to impact millions of patients with asthma and COPD around the world."

"We are pleased to partner with Propeller to develop the next generation of connected inhalers," said Salim Haffar, president of Aptar Pharma. "We believe the combination of Aptar's expertise and technology in inhaler design and development with Propeller's proven system for asthma and COPD patient management creates a compelling offer to meet the needs of stakeholders in this market place."

Aptar Pharma is part of the AptarGroup, Inc., family of companies, along with Aptar Beauty + Home and Aptar Food + Beverage. The company creates innovative drug delivery systems that meet the evolving needs of biotechnology, healthcare, and pharmaceutical companies around the world. Aptar Pharma provides customers with a wide range of delivery technologies and analytical services backed by decades of proven expertise. AptarGroup is headquartered in Crystal Lake, Illinois, United States, with manufacturing facilities in North America, Europe, Asia, and South America. For more information, visit www.aptar.com/pharma.

Founded in 2010, Propeller is the leading digital health platform in respiratory medicine. The company has received FDA 510(k) class II clearance to measure and improve medication adherence, predict exacerbations, and help reduce the frequency of symptoms and exacerbations in asthma and COPD. Propeller's platform has been clinically validated in two randomized controlled trials and more than 10 clinical studies involving over 1,400 patients. It has been used by patients with asthma or COPD in over 35 commercial programs across the United States at major healthcare systems, payers, employers, and other commercial partners. Propeller is backed by Safeguard Scientifics (NYSE: SFE), Social Capital, California HealthCare Foundation, Kapor Capital and other investors, and has been recognized by the TEDMED Innovation Showcase, White House Champion of Change, Bluetooth Breakthrough Product awards, and others. Visit http://propellerhealth.com/contact/ for more information.

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Rani Therapeutics Completes Latest Round of Funding, Brings Total Investment to $70M

PRNewswire: February 24, 2016 – SAN JOSE, CA, U.S.A. – Rani Therapeutics announced today that it has closed its latest round of funding, bringing the company's total investment to more than $70 million. New investors include AstraZeneca, Virtus Inspire Ventures, and Ping An Ventures. Existing investors in Rani Therapeutics include Novartis, Google Ventures, Buttonwood, GF Ventures, KPC Pharmaceuticals, InCube Ventures, and VentureHealth, among others. The funding will support expansion of the team, new facilities, and manufacturing scale up.

Rani, founded in 2012 and spun out of InCube Labs, is developing a novel technology platform to convert injectable drugs such as TNF-alpha inhibitors, interleukin antibodies, basal insulin, and GLP-1 into oral pills. In the last year, the company has entered into strategic collaborations with Novartis and Astra Zeneca/MedImmune to test its platform with selected drugs.

"We developed Rani Therapeutics with a clear vision—give patients suffering from chronic illnesses a convenient, easy and painless alternative to subcutaneous injections," said Mir Imran, chairman and CEO of Rani Therapeutics. "Our team has created a breakthrough drug delivery platform supported by a solid patent portfolio and that is what is attracting potential partners and investors. We are pleased with our progress and are now laser focused on demonstrating value for a variety of therapies."

"Delivering biologics orally would have a tremendous impact on patients, especially for those suffering from chronic diseases that require them to regularly take medications," said Jiang Zhang, managing director, Ping An Ventures. "Rani is developing a revolutionary platform, and we are very excited to support the company in this exciting next phase."

As part of its next stage of growth, Rani recently hired Robert Gaffney as vice president of operations to lead the company's expansion. Gaffney joined from Spinal Modulation, an InCube Labs company acquired by St. Jude Medical in 2015, where he served as chief operating officer.

Rani Therapeutics has developed a novel approach for the oral delivery of peptides, proteins, and therapeutic antibodies which to date can only be delivered through injections. The approach and technology for Rani Therapeutics was 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.

Novaliq Begins Phase 2 Clinical Trial of CyclASol® for the Treatment of Moderate to Severe Dry Eye Disease

Business Wire: February, 16, 2016 – HEIDELBERG, Germany – Novaliq GmbH, a pharmaceutical company with a disruptive drug delivery platform that transforms poorly soluble drugs into effective therapeutics for ophthalmology, today announced that it has begun enrolling patients in a phase 2 clinical trial that will evaluate the safety, efficacy and tolerability of CyclASol® for the treatment of moderate to severe dry eye disease (DED). CyclASol is a clear, preservative free ophthalmic solution of cyclosporine in SFA (semifluorinated alkanes).

This phase 2 study is a randomized, double-masked, placebo-controlled, multi-center trial, designed to evaluate the safety, efficacy, and tolerability of topical CyclASol for the treatment of moderate to severe DED. Patients will be randomized to one of four treatment groups that include two CyclASol groups, a placebo (vehicle control) group and an open label cyclosporine A 0.05% ophthalmic emulsion group. Study subjects will self-administer one drop twice daily, returning for examination periodically and at the end of the trial at four months. The study is being conducted in approximately four sites in the United States, and total planned enrollment is 200 patients.

"CyclASol is differentiated from other cyclosporine containing treatments for dry eye due to its innovative vehicle," said George Ousler, vice president of Dry Eye at Ora, Inc. "In a murine model of DED, CyclASol was shown to be at least equally effective but with a significantly faster therapeutic response compared to commercially available cyclosporine and dexamethasone products. Furthermore, the clinical phase 1 data has demonstrated excellent tolerability."

"The initiation of this phase 2 trial is an important step in advancing our clinical development plan," said Bernhard Günther, managing director and CEO of Novaliq GmbH. "In 2015, we made our footprint in the OTC dry eye market with the successful European launch of NovaTears®. Given the lack of treatment options currently available for patients with more severe DED, there is a need for novel, non-blurring, non-irritating, and preservative- and water-free formulations."

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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 EyeSol® technology enhances the topical bioavailability, stability, and safety of traditionally insoluble or unstable drugs improving the delivery, efficacy, and convenience of treatments for ocular surface diseases including dry eye through preservative-free and multi-dose 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.

Braeburn Pharmaceuticals and Knight Therapeutics Announce Canadian Sublicense Agreement for Probuphine®

PRNewswire: February 1, 2016 – PRINCETON, NJ, U.S.A. and MONTREAL, Canada – Braeburn Pharmaceuticals, Inc. ("Braeburn") and Knight Therapeutics Inc. (TSX: GUD) ("Knight"), a leading Canadian specialty pharmaceutical company, announced today that they have entered into an agreement whereby Knight received the exclusive rights to commercialize Probuphine® in Canada. Probuphine is an investigational subdermal implant designed to deliver buprenorphine continuously for six months following a single treatment, promoting patient compliance and retention as well as helping to prevent accidental pediatric exposure. Under the terms of this sublicense agreement, Knight will also handle all ongoing regulatory and commercial activities for Probuphine in Canada.

"According to the Canadian Drug Policy Coalition, overdose deaths from opioids have risen sharply in Canada and now account for approximately half of all drug related deaths in the country," said Behshad Sheldon, president and CEO of Braeburn. "Partnering with Knight Therapeutics is another step in our vision to making a lasting impact on how this chronic disease is treated in North America."

"We are pleased that we can be instrumental in bringing Probuphine® to Canada," said Jonathan Ross Goodman, president and chief executive officer of Knight. "Once approved by Health Canada, Probuphine® will be the first product to offer treatment for opioid addiction for six months following a single treatment. This innovative product has the potential to address an important unmet need for opioid dependent patients."

Probuphine is an investigational subdermal implant designed to deliver buprenorphine continuously for six months following a single treatment, and to promote patient compliance and retention. Buprenorphine, which is the active ingredient in multiple approved drug products for the treatment of opioid dependence, is currently available in sublingual and buccal formulations that require self-administration by patients on a daily basis.

Probuphine was developed using ProNeura™, the continuous drug delivery system developed by Titan Pharmaceuticals, Inc. ("Titan") that consists of a small, solid implant made from a mixture of ethylene-vinyl acetate (EVA) and a drug substance. The resulting construct is a solid matrix that is placed subdermally, normally in the upper arm in an outpatient office procedure, and removed in a similar manner at the end of the treatment period. Titan licensed the rights to commercialize Probuphine in the United States and Canada in 2012.

The efficacy and safety of Probuphine has previously been studied in several clinical studies. The most recent study enrolled 177 subjects who were randomized to receive either the Probuphine implants or sublingual tablets, for a treatment period of six months. Subjects in one group received four Probuphine implants plus daily placebo sublingual tablets. A second group received four placebo implants plus daily sublingual buprenorphine/naloxone tablets (≤8 mg/day).

The study met its primary objective of showing non-inferiority based on comparison of the proportion of treatment responders in each treatment arm. A responder was defined as having at least four out of six months free of illicit opiates based on urine testing and subject self-report. Additional analyses consistently demonstrated that Probuphine was non-inferior to sublingual buprenorphine/naloxone arm.

Braeburn, an Apple Tree Partners company, is a pill-free pharmaceutical company delivering precision medicine in neuroscience. In September 2015, the U.S. 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. On January 12, 2016, the FDA Psychopharmacologic Drugs Advisory Committee recommended approval by a vote of 12 to 5. The agency has 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

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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 www.braeburnpharmaceuticals.com.

Knight Therapeutics Inc., headquartered in Montreal, Canada, is a specialty pharmaceutical company focused on acquiring or in-licensing innovative pharmaceutical products for the Canadian and select international markets. Knight Therapeutics Inc.'s shares trade on TSX under the symbol GUD. For more information about Knight Therapeutics Inc., please visit the company's web site at www.gud-knight.com or www.sedar.com.

OptiNose® Announces Pipeline Project to Evaluate Nose-to-Brain Application of Bi-Directional™ Breath Powered® Technology Selected for Norwegian Government Funding

Business Wire: February, 1, 2016 – YARDLEY, PA, U.S.A. – OptiNose Inc., a privately held Delaware specialty biopharmaceutical company, today announced that its Norwegian affiliate (OptiNose AS) was selected to receive up to NOK 15.9 million (USD $1.8 million) by the Research Council of Norway to study its unique nasal drug delivery technology in the treatment of narcolepsy. The OptiNose proposal was one of 50 company projects selected from among 181 applications submitted to the Research Council's program for user-driven, research-based innovation research. Subject to successful contract negotiations with the Research Council and project partners, OptiNose would be able to use this research grant to help defray the cost of investigating "nose-to-brain" activity of Orexin-A delivered using patented OptiNose Bi-Directional Breath Powered delivery technology for the treatment of narcolepsy. Partners who have agreed to collaborate with OptiNose in the project include the Norwegian Centre of Expertise for Neurodevelopmental Disorders and Hypersomnias at Oslo University Hospital (OUS-NevSom), Hovione Farma Ciencia SA, Lisbon, Portugal, and Smerud Medical Research, Oslo, Norway.

"The opportunity to further investigate nose-to-brain drug transport in an effort to develop a new and much needed treatment for narcolepsy is very exciting," said Per G. Djupesland, M.D., Ph.D, chief scientific officer of OptiNose AS. "Narcolepsy is a chronic neurological disorder caused by destruction of neurons in the brain that produce Orexin-A, a neuropeptide regulating sleep and wakefulness. Currently available drugs primarily target the symptoms of narcolepsy and have many side effects. Patients suffering from narcolepsy experience excessive daytime sleepiness, disturbed nocturnal sleep, and episodes of sudden muscle paralysis triggered by emotions. We hope to advance the science and generate positive outcomes by directing treatment closer to the root of the problem by using Orexin-A powder delivered with our innovative exhaler device."

"2016 is off to an exciting start. We continue to advance both our near-term assets and our early-phase projects for conditions where there is real need for improved treatments," added Peter Miller, chief executive officer of OptiNose. "We have invested in research and development of novel therapies with significant differentiation, and we are pleased the Research Council of Norway believes it could be valuable to support this new project." ■