CRS Leading Delivery Science and Technology

Newsletter

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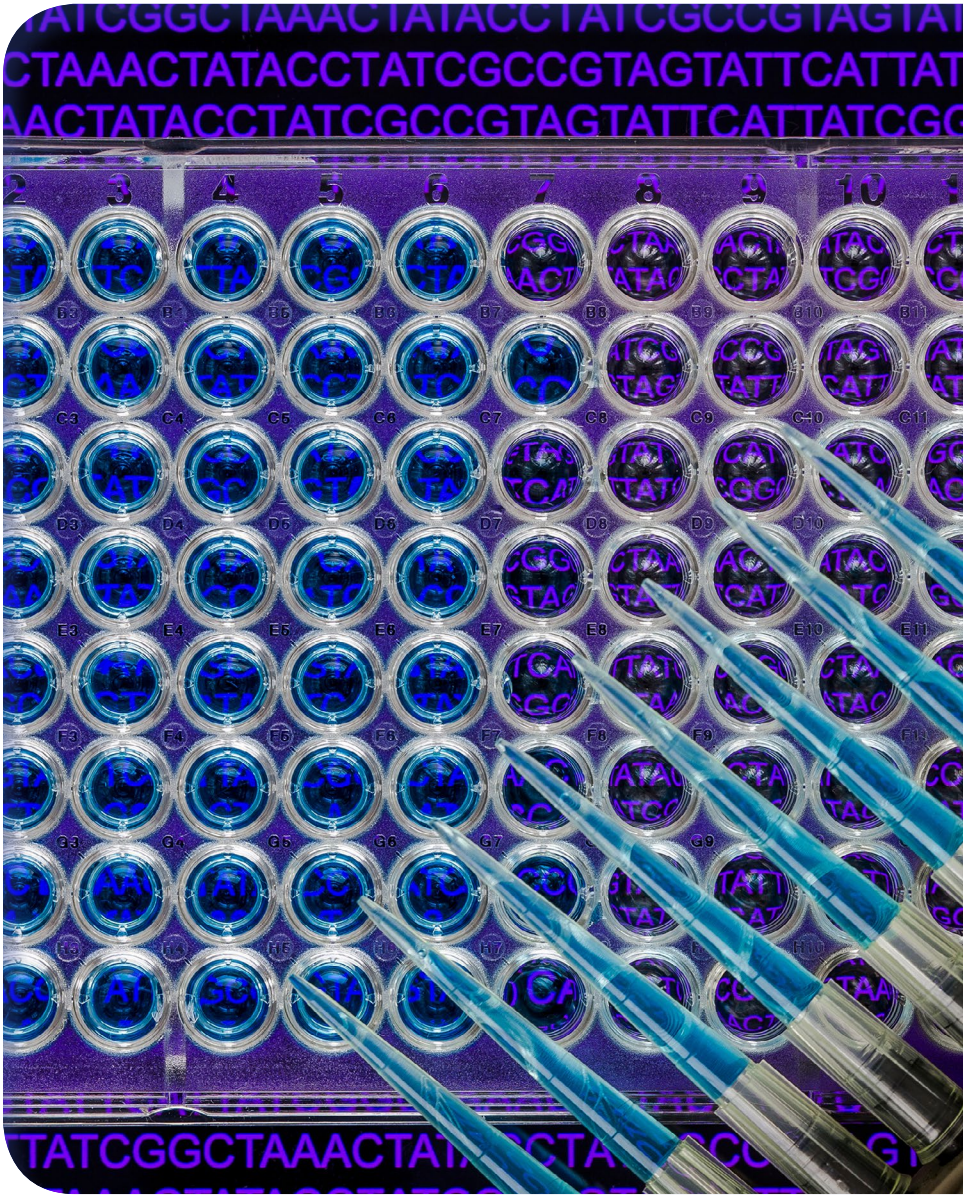

2017 Controlled Release Society Annual Meeting & Exposition

July 16–19, 2017
Sheraton Boston Hotel
Boston, Massachusetts, U.S.A.

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Cover image: A 96-well plate with samples with a nucleic acid sequence background.
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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.

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

Telephone: +1.651.454.7250
Facsimile: +1.651.454.0766

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

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

Arlene McDowell
University of Otago
New Zealand

Like Moths to a Flame

I went to an art auction last night with the theme of moths. Why moths? A friend set up MothNet as a citizen science project to engage the public in science through discovering the beauty and importance of moths (twitter.com/mothNetNZ). I learned that most of New Zealand's moths occur nowhere else in the world. The auction was to raise money to assist school children from New Zealand to attend the World Indigenous Peoples Conference on Education in Canada. The students will be presenting research they have done on New Zealand moths as part of MothNet. What a fantastic cause.

I believe there is huge value in supporting the next generation of scientists, and it got me thinking how CRS is an organization that similarly does a great job in supporting emerging scientists. One example of this is the new "CV on a Poster" initiative at the 2017 CRS Annual Meeting in Boston, which is designed to give our student and postdoc attendees the opportunity to engage with recruiters, and it looks like a great opportunity. The annual meeting is also where the *CRS Newsletter* editors select articles for the *CRS Newsletter*. If you are invited to write up your poster as an article for the *CRS Newsletter*, please take up this opportunity to give your work greater exposure. If you are not able to make the meeting in Boston, you can catch some of the highlights in the next issue of the *CRS Newsletter*.

As you read in the final issue for 2016, Yvonne Perrie has stepped down from her role of editor and chair of the *CRS Newsletter* Committee after 12 years of fantastic service. Charles Frey has also stepped down, and his contribution to the Patent Watch section of the *CRS Newsletter* will be greatly missed. We say a huge thank you to Yvonne and Chuck for their considerable input over many years. I would also like to extend a warm welcome to the new committee members who have joined the *CRS Newsletter* team: Ken Carson (Southwest Research Institute, U.S.A.), Ryan Donnelly (School of Pharmacy, Queen's University, Belfast, Ireland), and Medha Joshi (Chicago College of Pharmacy, Midwestern University, U.S.A.).

In case you were wondering, I was restrained and only bought two pieces of art at the moth auction!

Best wishes,

Arlene McDowell ■

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Get more from the annual meeting by including a highly focused premeeting educational workshop. You also have the option of registering for a workshop without registering for the annual meeting.

Seats are limited, so don't wait! Register today at **controlledreleasesociety.org**.

Saturday, July 15

Novel Delivery Platforms: Penetration Transdermal Delivery Systems and Oral Delivery Systems

8:00 a.m. – 1:30 p.m.

Sponsored by CHEMISTRY HOLDINGS

This workshop will focus on development of novel delivery platforms, highlighting new innovative technologies, and bringing innovative products to the market. The workshop will feature new innovative transdermal penetration technology that has been developed that is a safe, effective, transient way to bring molecules through the skin, scalp, and nail, and how that technology has been brought to the market. It will also focus on novel biogel transdermal delivery technology, innovative transdermal drug delivery systems, and new oral spray delivery systems.

Student/Postdoc registration: $175
Regular registration: $225

Basic Concepts of Oral Drug Delivery: What You Need To Know

9:00 a.m. – 5:00 p.m.

Sponsored by Colorcon Innopharma technology

Members of CRS often comment that the society has helped them in many ways, but first and foremost in exposing them to the collective knowledge of its members. Newcomers usually find the first meetings confusing, in particular if they are used to "focused" meetings. As an example, a polymer scientist developing a product that might be useful in the controlled release context might have little or no knowledge about the physiological conditions his/her polymer might encounter after ingestion. Conversely, a clinician with a problem that may be solved with controlled release might know little or nothing about materials sciences or controlled release technologies. This workshop attempts to give an oversight covering the "usual (known to us) unknowns."

Registration: $179

Entrepreneurship and What You Need To Know

1:00 – 5:00 p.m.

Organized by the CRS Young Scientist Committee

Sick of writing job applications and doing interviews? How about employ yourself and bring your ideas to life by turning them into useful products! This workshop will give you the chance to meet entrepreneurs who have started their own companies. Come and hear true stories about the ups and downs, gain valuable insights into what is required to drive this exciting opportunity, and get guidance on how to start up your own research. Be inspired by the Boston entrepreneurial spirit, and maybe this could be your first step in building the next disruptive platform in health and medicine.

Young Scientist Events are organized to meet the needs of young scientists. This workshop is free, and it is now full.

continued

Sunday, July 16

Enabling Successful Liposomal Formulation from Scratch – Lipid Synthesis, CMC, Regulatory and Case Study
8:00 a.m. – 1:00 p.m.

Sponsored by MilliporeSigma POLYMUN SCIENTIFIC

During the last decade, liposomes and lipid nanoparticles have been increasingly used in clinical trials, especially in the fields of oligonucleotide delivery, as vaccine carriers, as solubilization aids and to minimize the side effects of cytotoxic drugs and prolong the circulation half-life of contrast agents. The development of these nonconventional drug delivery systems remains nowadays very challenging.

In this workshop, experts on the different development stages will share their knowledge on how to best face these challenges. Topics to be covered are: process development and GMP manufacturing of lipids, lessons learned from liposomal products and processes - chemistry, manufacturing and controls, driving biomedical innovation by advancing FDA's Science alliance, and development of a small activating RNA (saRNA) encapsulated in a SMARTICLE® liposomal formulation for treatment of liver disease including hepatocellular cancer.

Registration: $179

Start Earlier, Move Faster: Smart Drug Development & Design from Candidate to Phase I
8:00 a.m. – 1:00 p.m.

Sponsored by Catalent

Today's scientists are under significant time pressure to accelerate their compound from discovery to the clinic. Such pressure can often lead research organizations to adopt short-term thinking and overlook the downstream realities of drug development. Addressing issues early and comprehensively in the development life cycle can result in fewer problems down the line such as escalating timelines, costs, and regulatory issues. It is important to leverage the skills and experience of experts and connect the dots between competencies to optimize the development pathway and enable drug candidates to reach their true potential.

This workshop will focus on a number of key considerations for transitioning a molecule from discovery to phase 1 readiness, including API and formulation development, pharmacokinetic and preclinical toxicology studies, and regulatory requirements.

Registration: $179

Gaining Your Career Edge: CV and Interview Techniques
9:00 a.m. - 12:00 p.m.

Organized by the CRS Young Scientist Committee

Have you just graduated? Are you transitioning from academia into industry? Entering the next phase of your career? This workshop will equip with you with the knowledge, skills, and mindset to overcome the rejection and obstacles that you could experience in today's tough job market. Learn CV and interview techniques that will help you gain an edge in your next application.

Young Scientist Events are organized to meet the needs of young scientists. This workshop is free, and it is now full. ■

Exploring Possibilities of Microneedles with Ryan Donnelly

Vishwas Rai[1] and Bozena B. Michniak-Kohn[2]

Donnelly in his lab.

Prof. Ryan Donnelly is the Chair of Pharmaceutical Technology at Queen's University, Belfast, U.K. He is a young and dynamic researcher in the field of transdermal delivery with primary focus on microneedle drug delivery and applications. Prof. Donnelly's research is centered on design and physicochemical characterization of advanced polymeric drug delivery systems for transdermal and topical drug delivery, with a strong emphasis on improving therapeutic outcomes for patients. The bioadhesive patch he developed during his Ph.D. studies was shown to be successful in the clinic for photodynamic therapy of over 100 patients with neoplastic and dysplastic gynecological conditions, and the patent was subsequently licensed to Swedish Pharma AB.

He secured a B.Sc. degree in pharmacy from Queen's University Belfast (1999) and a Ph.D. in pharmaceutics from the same institution (2003). He carried out a short (3 month) period of postdoctoral research focused on delivery systems for photosensitizers and was appointed as a Lecturer in pharmaceutics at the School of Pharmacy in January 2004. He was promoted to Senior Lecturer in 2009, Reader in 2011, and Chair in Pharmaceutical Technology in 2013.

Prof. Donnelly's current research is focused on novel polymeric microneedle arrays for transdermal administration of "difficult-to-deliver" drugs and intradermal delivery of vaccines and photosensitizers. His research work has gained a lot of attention and interest in the academic and industrial community and has been funded by the Biotechnology and Biological Sciences Research Council (BBSRC), Engineering and Physical Sciences Research Council, Medical Research Council, Wellcome Trust, Royal Society, and pharmaceutical and medical devices industries.

At graduation with Prof. Brendan Gilmore (left) and pharmacy graduate Emma McAlister (center), who is now a second year Ph.D. student in Donnelly's group.

He has authored over 500 peer-reviewed publications, including several granted patents, five textbooks, and approximately 160 full papers. He has been an invited speaker at numerous national and international conferences. Prof. Donnelly is the editor-in-chief of *Recent Patents on Drug Delivery & Formulation* and a member of the editorial advisory boards of *Micromachines*, *Pharmaceutical Technology Europe*, *Expert Review of Medical Devices*, and *Journal of Pharmacy & Bioallied Sciences* and is a visiting scientist at the Norwegian Institute for Cancer Research, where he is an associate member of the Radiation Biology Group.

He won the Controlled Release Society Young Investigator Award in 2016, the BBSRC Innovator of the Year Award and the American Association of Pharmaceutical Scientists *Pharmaceutical Research* Meritorious Manuscript Award in 2013, the GSK Emerging Scientist Award in 2012, the Royal Pharmaceutical Society's Science Award (2011), the Queen's Improvement to Society Award (2011), an Innovation Leader Award from the NHS Research & Development Office (2009), a research scholarship from the Research Council of Norway (2004), and the Pharmaceutical Society of Northern Ireland's Gold Medal in 1999. In 2013, he was listed in the 40 most influential business leaders in Northern Ireland under the age of 40 by Belfast Media Group.

Prof. Donnelly can be contacted directly at r.donnelly@qub.ac.uk.

Q *What was your research focus during your Ph.D. and your postdoctoral studies?*

A My Ph.D., supervised by Dr. Paul McCarron and Prof. David Woolfson, focused on design, development, and small-scale manufacture of bioadhesive patches intended for enhanced delivery of 5-aminolevulinic acid (ALA) to neoplastic and dysplastic vulval lesions. Patients will not die from these diseases, but symptoms can be extremely distressing. Surgical excision can be mutilating, leading to loss of function and subsequent psychological problems. In photodynamic therapy based on ALA, the precursor causes accumulation of the potent photosensitizer in target tissues, which are then destroyed selectively by illumination with red light, which generates reactive oxygen species through interaction with the accumulated photosensitizer. ALA was at

continued

[1] Independent consultant, 39206 Guardino Drive, Fremont, CA, U.S.A.
[2] Ernest Mario School of Pharmacy, Rutgers–The State University of New Jersey, U.S.A.

With colleagues Fiona Kirkpatrick (left) and Lynne Cairns (right) at the pharmacy students' formal dinner.

the time being delivered using an extemporaneously prepared cream, which had to be refrigerated due to the drug's instability. Patients had to be immobilized and catheterized for 6 hours to allow drug absorption and photosensitizer accumulation. This leads to unnecessary distress. My task was to produce a flexible patch that would adhere strongly in a moist environment in ambulatory patients and have a water-impermeable backing layer to allow normal micturition and bowel opening. The biggest challenge was preventing the high drug loading in the water-based patch from crystallizing during drying. I achieved this by producing very thin drug-loaded films. These dried in minutes rather than days and were then laminated multiple times to produce the required patch thickness and drug loading per unit area. This was a new way for making water-based bioadhesive patches and enabled me to respond at short notice to requests from the Belfast City Hospital, where the patients were being treated in clinical trials led by consultant gynecologist Dr. Agnieszka Zawislak. We saw symptomatic improvement in all of the patients treated, with the histological grade of vulval intraepithelial neoplasia being reduced in over half of the patients in that cohort treated. We filed a patent on the method of patch production, and it has now been granted in Australia. The company the university licensed the patent to, Swedish Pharma AB, sees it as a potential improvement on commercially available creams used in photodynamic therapy of basal cell carcinoma of the skin, which is the most common cancer in Australia. Swedish Pharma is still raising funds to take the technology forward, so unfortunately patients are not yet benefitting from this delivery system.

As for my career as a postdoc, it was very short—just three months. Indeed, I had only been in the post for a matter of weeks when I was offered a lectureship. To say that led to a steep learning curve would be an understatement. Embarking on an independent academic position at the age of 25 with little postdoctoral experience was quite an undertaking. I made a lot of early mistakes, but I learned something from them all and benefitted greatly from the continued support of my former Ph.D. supervisors and also Prof. Johan Moan at the Norwegian Radium Hospital, whose lab I had the opportunity to work in during the first summer I was in post as a lecturer.

My early work as a lecturer focused on enhancing delivery of drugs used in photodynamic therapy, and this led me to microneedles. Since photodynamic therapy is quite a niche treatment, it was difficult to get funding, and so I broadened the scope of my microneedles research to look at enhanced transdermal drug delivery and minimally invasive patient monitoring and diagnosis.

Q *What happened next? Where did you go from there?*

Donnelly with a microneedles model.

A Upon deciding to focus on microneedles, I quickly realized that this was a field principally focused on delivery of vaccines and highly potent drugs of biological origin. Most conventional drugs, however, have daily doses in the range of tens to hundreds of milligrams per day. Small postage stamp-sized microneedle patches coated with drug would not be capable of delivering clinically effective doses. Something very different was required. I came up with hydrogel-forming microneedles prepared from crosslinked FDA-approved polymers. Such microneedles contain no drug themselves, but they rapidly swell through uptake of skin interstitial fluid upon insertion. This allows continuous, controllable delivery of high drug doses from an attached drug-containing layer, the properties of which can also be modulated to optimize the kinetics of delivery. Importantly, such microneedles are removed from skin intact, leaving no measurable polymer residue behind. This phenomenon led to another idea: using such microneedles to capture skin interstitial fluid and its contents for use in patient monitoring and diagnosis.

Q *Besides microneedles, are you interested in pursuing other R&D ventures? What is your inspiration?*

A My group is currently focused exclusively on microneedle research. We have several projects focused on delivery of high drug doses for a range of applications. I am confident that the technologies we have developed can greatly expand the range of drugs that can be effectively delivered through the skin. We also have a large program on microneedle systems with applications in global health and have just started a significant collaboration with a major biosensors company.

As a registered pharmacist, my inspiration is taken from patient need. I strive to develop delivery systems and blood-free monitoring and diagnostic tools that will improve therapeutic outcomes, not only for patients in the Western world but also in the world's poorest countries.

continued

Q *Please share a few of the most important research publications coming out of your research lab and their impact on the field.*

A We have recently shown that the larger microneedle patches that will be required to deliver high drug doses can be as efficiently applied to skin as conventional small patches:

Ripolin, A, Quinn, J, Larrañeta, E, Vicente-Perez, EM, Barry, J, Donnelly, RF. Successful application of large microneedle patches by human volunteers. Int. J. Pharm. 521: 92-101 (2017).

If a patient is being treated with a microneedle patch that is delivering a drug the patient needs every day, then repeated microneedle application must cause no skin problems or other detrimental effects for the patient. Our recent mouse study suggests that repeated microneedle application will be very safe:

Vicente-Perez, EM, Larrañeta, E, McCrudden, MTC, Kissenpfennig, A, Hegarty, S, McCarthy, HO, Donnelly, RF. Repeat application of microneedles does not alter skin appearance or barrier function and causes no measurable disturbance of serum biomarkers of infection, inflammation or immunity in mice *in vivo*. Eur. J. Pharm. Biopharm. doi: 10.1016/j.ejpb.2017.04.029 (*In press*).

Q *Please share some publications from fellow researchers that have had the most influence in shaping the related pharmaceutical field.*

A My own career has been very much shaped by the positive influence of outstanding academics like David Woolfson, Sandy Florence, Richard Guy, Adrian Williams, Johan Moan, Michael Hamblin, and Robert Lochhead, all of whom have been generous with their time, advice, and support. Duncan Craig was an inspirational figure during his time in Belfast, and I learned much from his strategic vision and how he managed his research group. From a product development viewpoint, Werner Wessling from LTS Lohmann has been an important teacher and a good friend.

Currently, I learn a lot from other researchers studying microneedles and transdermal delivery in general. In my view, the following papers are of high current importance:

Rzhevskiy, AS, Guy, RH, Anissimov, YG. Modelling drug flux through microporated skin. J. Controlled Release 241:194-199 (2016).

Arya, J, Henry, S, Kalluri, H, McAllister, DV, Pewin, WP, Prausnitz, MR. Tolerability, usability and acceptability of dissolving microneedle patch administration in human subjects. Biomaterials 128:1-7 (2017).

Lee, KT, Coffey, JW, Robinson, KJ, Muller, DA, Grøndahl, L, Kendall, MA, Young, PR, Corrie, SR. Investigating the effect of substrate materials on wearable immunoassay performance. Langmuir 33: 773-782 (2017).

Q *What are your current career aspirations?*

A As a pharmacist, I would like to see microneedle technologies developed by my group reaching the market and being used to help patients. I think big pharma has traditionally seen microneedles as something that would only be useful for vaccination in the developing world, and so money could not be easily made on such products. This has clearly slowed development and clinical translation. However, our work, and that of some others, will hopefully begin to change minds soon. It is only with suitable investment to scale up manufacture and address regulatory questions that microneedles will ever realize their undoubted potential.

In terms of my leadership role in the university, I am director of a new interdisciplinary research initiative that aims to enhance collaboration between researchers in pharmacy, chemistry, engineering, medical sciences, and computing. We hope to boost research productivity and impact by addressing a range of global challenges.

Preparing for a soccer match.

Q *What are some things you enjoy in your personal life?*

A I really enjoy my job. Indeed, if I hadn't become a pharmacist and research scientist, there are only a few things that would have appealed to me: a professional soccer player or nightclub DJ! I still play soccer every week with colleagues from the School of Pharmacy and have recently re-signed with Carrickmacross Rovers, the club in County Monghan in Ireland that I played with for many years as a schoolboy and during my undergraduate and postgraduate degrees. I live outside Warrenpoint in County Down, a small and beautiful seaside town. My wife, Johanne, and I like walking in the countryside and along the seafront in Warrenpoint when we're not teaching pharmacy; Johanne is also a pharmacist and teaches pharmacy practice at Queen's as well as working for Boots in community pharmacy. ■

Hydrogel Sheet Consisting of PEG-*g*-Chitosan and Drug Carriers: An Approach to Constructing Functional Biomaterials with Controllable Drug-Release Properties

Tomoki Ito, Taku Takami, and Yoshihiko Murakami[a]
Department of Organic and Polymer Materials Chemistry, Tokyo University of Agriculture and Technology, Japan

A wound on the surface of biological tissue heals through complex processes that involve three phases: inflammation, proliferation, and maturation. In these phases, proteins including blood coagulation factors and growth factors play an important role. Growth factors are proteins that control the growth, differentiation, and metabolism of cells and regulate the process of tissue repair.[1] Wound-dressing "sheets" can cover wound sites and enhance wound healing. Fluid at the wound site is an important reservoir of growth factors that promote the wound healing process,[2] and thus, conventional dry wound-dressing materials (such as gauze) often hinder wound healing by absorbing exudates including macrophages and growth factors. To overcome these defects, wound-dressing "hydrogels" have functioned to prevent wound-site desiccation and microbial invasion and to maintain the activity of growth factors.[3,4]

The controlled sustained release of drugs from hydrogels is difficult because the release mechanism depends mainly on two phenomena: the degradation of polymeric networks and the diffusion of compounds through the hydrogel medium. In these regards, we have developed a novel hybrid approach for the construction of biomaterials for drug delivery systems: the incorporation of drug carriers (polymeric micelles) into base materials (such as gel[5–7] and sheets[8,9]). Polymeric micelles consisting of amphiphilic block copolymers have a three-dimensional core-shell structure (a solid hydrophobic core and a hydrophilic shell) in an aqueous solution. The micelles can release hydrophobic drugs by means of either dilution-induced collapse or the degradation of micelle-forming polymers. Thus, hybrid-material designs (i.e., the incorporation of micelles into hydrogels) should help give the hydrogels various controllable drug-release properties.

Chitosan, a linear copolymer of β-(1-4)-linked 2-acetamido-2-deoxy-β-D-glucopyranose and 2-amino-2-deoxy-β-D-glycopyranose (*N*-deacetylated derivative of chitin as a main component of the exoskeleton of crustaceans), has various biomedical and pharmaceutical applications because of its potential beneficial properties such as its biodegradability, nontoxicity, antimicrobial activity, and reinforcement of wound healing. These properties have resulted in the use of chitosan as a raw compound for wound-dressing materials.[10,11] However, strong intermolecular hydrogen bonds on chitosan backbones make the chitosan rigid, insoluble, and resistant to the construction of chitosan hydrogels. One of the most effective ways to address these problems is to perform polymeric modification, which improves chitosan's molecular characteristics.

Figure 1 shows our strategy for designing a novel chitosan–polymeric micelle hybrid hydrogel sheet.[12] The hydrogel consists of poly(ethylene glycol) (PEG)-*graft*-chitosan (PEG-*g*-chitosan) and crosslinkable polymeric micelles (aldehyde-terminated polymeric micelles consisting of PEG-polylactide block copolymers). The preparation of PEG-*g*-chitosan serves to increase the solubility and improve the biocompatibility of the chitosan. Although there have been numerous studies on PEG-*g*-chitosan and its use in biomaterials, the characteristic feature of our PEG-*g*-chitosan–polymeric micelle hybrid gel sheet is that only polymeric micelles were used as crosslinkers for gelation. It is expected that this structural feature will give the sheet controllable drug-release properties.

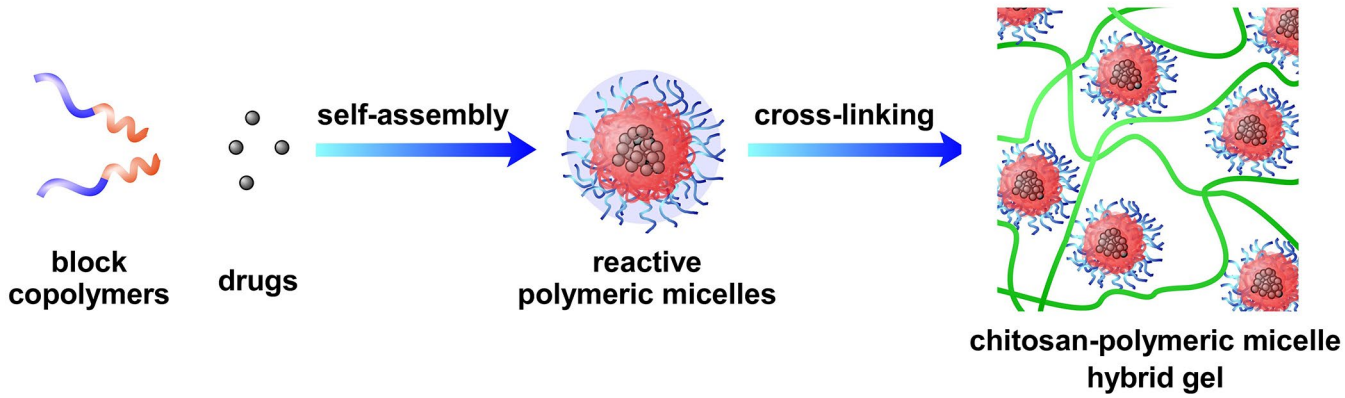

Figure 1. *The strategy for designing a novel chitosan–polymeric micelle hybrid hydrogel sheet. The hydrogel consists of PEG-graft-chitosan (PEG-g-chitosan) and crosslinkable polymeric micelles.*

continued

[a] Corresponding author. E-mail: muray@cc.tuat.ac.jp

Hydrogel was not obtained when only PEG-*g*-chitosan was present, whereas hydrogel was rapidly obtained when PEG-*g*-chitosan was mixed with aldehyde-terminated polymeric micelles. The results show that block copolymers form micelles to crosslink with PEG-*g*-chitosan. Figure 2 shows an obtained hydrogel sheet from mixed solutions containing either PEG-modified chitosan or reactive polymeric micelles (if necessary, one can select the appropriate support medium, such as polyvinylidene chloride film, when the sheet is prepared). After the sheet completely dried, it was rigid and thin—and was expected to be suitable for stable preservation. After immersing the dried sheet in water, we successfully obtained a flexible hydrogel sheet, as shown in Figure 2. The hydrogel can be reversibly dried and moistened without a collapse taking place. Figure 3 shows the time course of the drug release from two types of hydrogel sheets: a sheet in which drugs were dispersed in the polymer networks and a sheet in which drugs existed only in the crosslinkers (polymeric micelles). Tetracycline (TET), an antibiotic used for treating infections in bones and soft tissues, served as a model drug in our study because the co-use of TET with wound dressing can increase healing efficiency.[13,14] TET was released from the hydrogel sheet in which TET existed only in the crosslinkers in a sustained manner. Thirty percent of the TET was released from the sheet after 50 h of incubation. Interestingly, we observed that the release of TET from the hydrogel sheet in which drugs were incorporated in the crosslinkers (polymeric micelles) was less than the release of TET from the hydrogel sheet in which drugs were dispersed in the polymer networks.

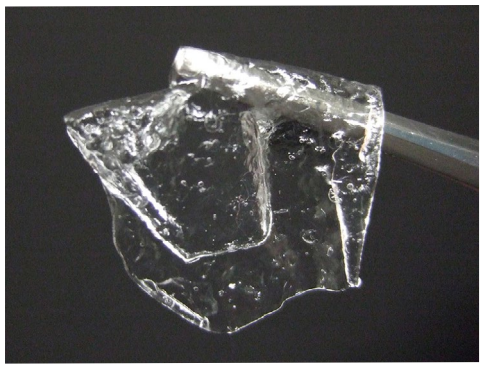

Figure 2. *The hydrogel sheet from mixed solutions containing either PEG-modified chitosan or reactive polymeric micelles.*

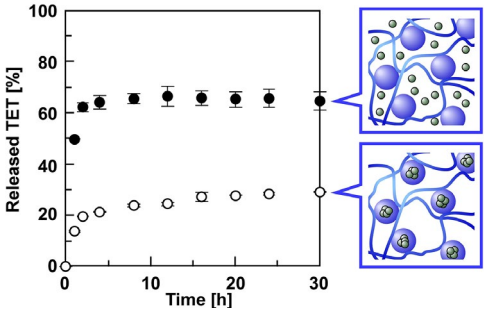

Figure 3. *The time course of the tetracycline (TET) release from two types of hydrogel sheets: a sheet in which TET was dispersed in the polymer networks (top) and a sheet in which TET existed only in the crosslinkers (polymeric micelles, bottom).*

We expected that the hydrogels that had formed from the polymeric micelles possessing a tightly packed (i.e., well-entangled) inner core would exhibit slower drug-release properties than would the hydrogels that had formed from the polymeric micelles possessing a loosely packed structure. Our research demonstrates that our strategy of incorporating drug carriers into materials might benefit the construction of biomaterials with controllable drug-release properties.

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Advances in Clinically Viable Lipid Nanoparticle Compositions for mRNA Delivery

K. Lam, J. Heyes, A. Judge, L. Palmer, H. Yuen, P. Schreiner, J. Bechard, and M. Abrams
Arbutus Biopharma, Burnaby, BC, Canada

Arbutus's lipid nanoparticle (LNP) platform is the leading nucleic acid delivery technology that is used in a number of drug products now in clinical development. LNPs comprise a mixture of neutral, cationic, and PEGylated lipids that can be formulated into a variety of compositions to confer the desired pharmacokinetic/biodistribution and pharmacodynamic properties onto the encapsulated nucleic acid. Currently, the most advanced LNP products are siRNA-based drugs that mediate their therapeutic effects through RNA interference (RNAi). These span a variety of indications including rare genetic disease (patisiran for transthyretin [TTR]-mediated amyloidosis, currently in phase III), infectious disease (TKM-HBV in phase II), and oncology (TKM-PLK1 in phase II). The LNP platform is also well suited to other classes of nucleic acid drugs, and we have demonstrated its utility for delivering mRNA. mRNA-LNPs enable very high expression levels of encoded therapeutic proteins after intravenous administration, and they are also highly effectively employed as mRNA vaccines, generating strong humoral and cellular immune responses against encoded antigenic proteins. We continuously seek to broaden the therapeutic index of the LNP platform, from both potency and tolerability perspectives, through formulation development. These efforts have led to a new generation of LNPs with optimized performance for mRNA delivery that are now ready for clinical development.

It is important to recognize that nucleic acid drugs can activate an immune response, including cytokine release, which can directly impact tolerability. Evidence for this has emerged from the large body of clinical safety data with siRNA-LNP products, for which dose-dependent, sporadic incidences of immune activation manifesting as mild infusion-related reactions (IRRs) have been observed. These types of reaction can be successfully managed with steroid premedication. However, it would be advantageous to address these drug properties at the compositional level in advance, by engineering LNPs and the encapsulated nucleic acid to reduce interactions with the immune system. This would be anticipated to substantially broaden the therapeutic index of the LNP platform.

We have developed new formulation strategies to address the challenge of immune stimulation. Initial activity and tolerability screens were evaluated with siRNA payloads in murine models. Primary screens conducted in mice have identified several LNP formulation strategies that dramatically attenuate cytokine release (Fig. 1A), while preserving or improving potency (as measured by RNAi activity or mRNA expression levels) compared with the benchmark formulations currently used in the clinic for siRNA delivery (Fig. 1B).

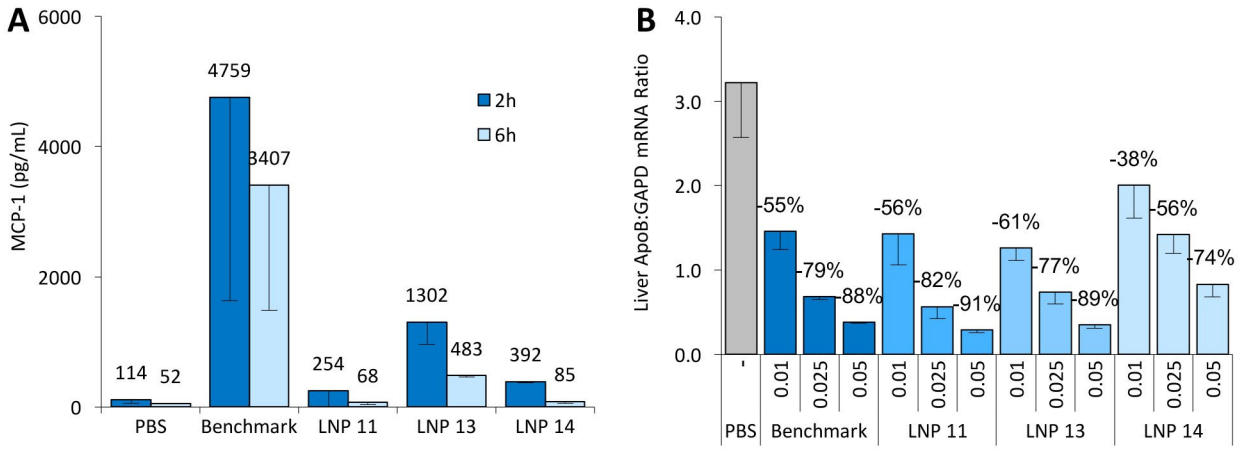
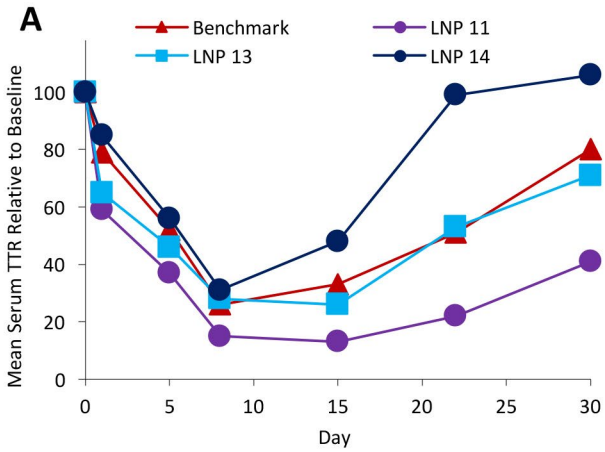


Figure 1. *Mouse primary screens identified LNP compositions of interest. (A) Immune stimulation: high doses (10 mg/kg) of LNPs were necessary to consistently detect an acute cytokine response in mice (n = 5,* ±SD*). Plasma samples assessed for cytokines at 2 and 6 h. Representative cytokine results (MCP-1) revealed that all three novel compositions induced substantially lower cytokine release than the benchmark control. (B) Potency: preliminary activity screening was performed in a mouse ApoB silencing model. Mice were administered LNPs at 0.01, 0.025, or 0.05 mg/kg i.v. and liver ApoB mRNA quantified by branched-DNA assay at 48 h post-administration (n = 3,* ±SD*).*

continued

Compositions of interest were then advanced into nonhuman primates (NHP). The NHP model has proved to be an excellent predictor of LNP potency for liver delivery in man. By using an siRNA targeting the endogenous gene target TTR, we have identified lead LNP compositions that are significantly more potent for liver delivery in NHP than those currently utilized in clinical formulations such as patisiran. Cynomolgus monkeys received LNPs via a 60 min IV infusion containing TTR siRNA dosed at 0.0375 mg/kg. By way of example, the novel formulation LNP 11 displayed excellent potency compared with a benchmark clinical formulation (Fig. 2A). To evaluate immune stimulation, animals were then administered LNPs at a dose high enough to cause cytokine release with benchmark formulations (2 mg/kg i.v.). In this context, LNP 11 was particularly well tolerated, triggering minimal cytokine release that was comparable to saline-treated controls (Fig. 2B). Given the additional improvement in potency, the increase in therapeutic index for this novel composition is predicted to be considerable.

Many approved liposomal drugs are associated with IRRs in the clinic: for example, Doxil (10–45% of patients), Ambisome (10%), and DaunoXome (14%). Pigs are a particularly sensitive species for these hemodynamic effects and have been proposed as an exaggerated model of IRRs that occur in a fraction of the human population.[1] We therefore utilized a telemetered pig model to assess hemodynamic changes and inflammatory responses after a single intravenous infusion of LNP. Hemodynamic changes such as pulmonary hypertension, decreased cardiac output, increased vascular resistance, and increased plasma thromboxane are prominent symptoms of IRRs in the pig. These changes were evident after infusion of a benchmark LNP with a similar composition to a current clinical formulation. By comparison, changes in all of these parameters were substantially reduced in animals treated with the novel LNP 11 composition (Fig. 3). Overall, comparison between the various animal models indicates that improvements from the new LNP formulation strategies translate well between species with respect to both potency and tolerability.



Improvements in LNP design, together with minor formulation and process changes tailored toward mRNA payloads, have been applied to the challenge of mRNA delivery. The resulting mRNA-LNPs have similar physicochemical characteristics to those encapsulating oligonucleotides, displaying a largely nonlamellar, electron dense morphology, as shown by cryo-transmission electron microscopy (Cryo-TEM, Fig. 4A). Intravenous injection of mRNA LNP results in high expression of the encoded protein, especially within hepatocytes, where near uniform mRNA expression is seen throughout the liver parenchyma (Fig. 4B).

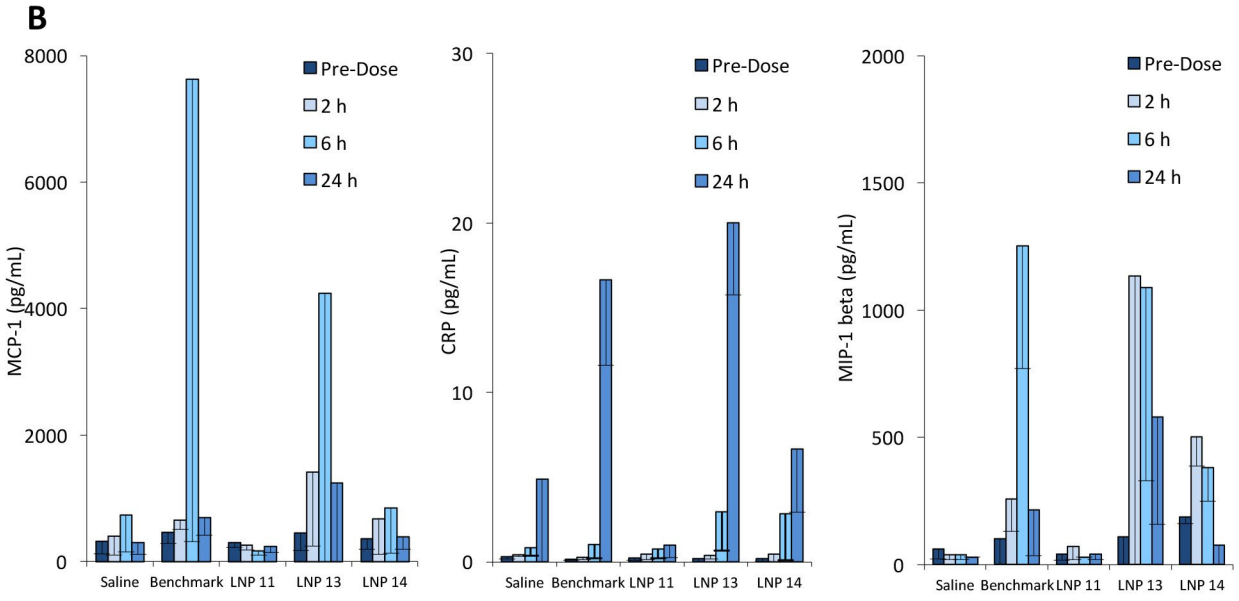


Figure 2. *Formulation improvements in NHP. Four LNP compositions containing TTR siRNA were administered to cynomolgus monkeys (n = 4) via 60 min intravenous infusion. (A) Potency: LNPs administered at a dose of 0.0375 mg/kg TTR siRNA and serum TTR protein levels assessed at regular time intervals to 30 days. (B) Cytokine release: LNPs administered at a dose of 2 mg/kg siRNA and serum cytokine release assessed at the indicated time points using a multiplex assay for 46 inflammatory biomarkers. MCP-1, MIP-1β, and C-reactive protein (CRP) are shown as representative examples.*

continued

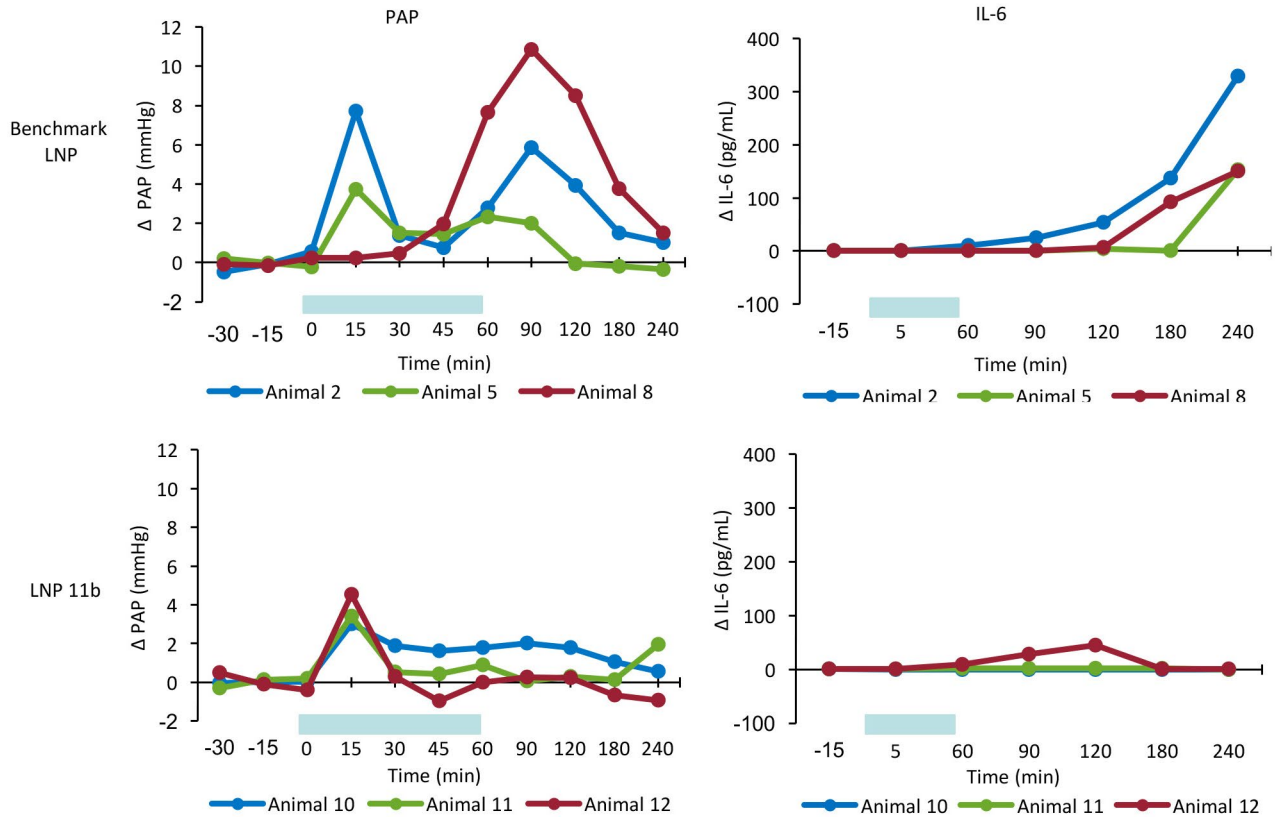


Figure 3. *Reduced symptoms of IRRs with novel LNP compositions in pigs. Two LNP compositions were administered by 60 min i.v. infusion to anesthetized, telemetered Gottingen minipigs (0.3 mg/kg siRNA; n = 3) and test article–related effects on hemodynamic parameters and inflammatory markers were evaluated. Pulmonary arterial pressure (PAP) and serum IL-6 are shown as representative parameters.*

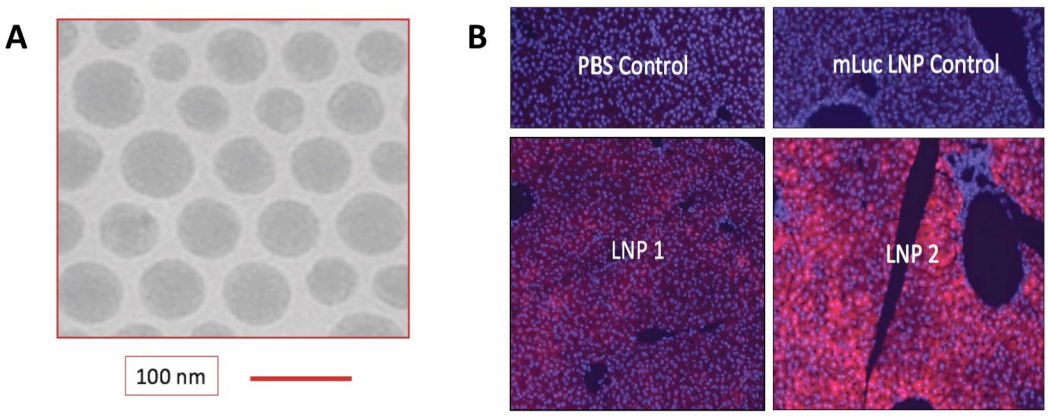


Figure 4. *LNPs with mRNA payloads. (A) Cryo-TEM image of mRNA-LNPs showing largely nonlamellar, electron dense morphology. (B) Hepatic expression of fluorescent mCherry protein (pink) after single i.v. injection of mCherry mRNA formulated in either LNP 1 or LNP 2 compositions (1 mg/kg). Cell nuclei stained blue (DAPI).*

continued

To establish the relative potency of mRNA-LNPs, we compared LNP formulations comprising either the aminolipid MC3 (analogous to the clinical patisiran formulation) or an LNP (termed LNP 2) that incorporates an alternate proprietary aminolipid that we have previously utilized in a clinical TKM-HBV product candidate. Using a murine erythropoietin (Epo) mRNA model, we determined that LNP 2 was approximately fourfold more potent than the MC3 LNPs (Fig. 5A), based on the level of plasma Epo protein expression after a single intravenous injection. These initial studies utilized standard, silica gel purified mRNA preparations that we and others have found to possess substantial immune-stimulatory activity, despite the incorporation of chemically modified uridine and cytodine nucleotides. As anticipated, therefore, these Epo mRNA-LNPs induced high cytokine release in mice (Fig. 5B). Remarkably, despite the quality of the mRNA payload, the incorporation of novel LNP design elements developed using siRNA-LNPs in the NHP and porcine models above (e.g., LNP 11 and the related compositions LNP 16 and LNP 17) greatly reduced cytokine release triggered by the Epo mRNA compared with either MC3 or LNP 2 compositions (Fig. 6). This marked improvement in tolerability was accompanied by high level Epo expression of similar or greater potency to LNP 2 (Fig. 6).

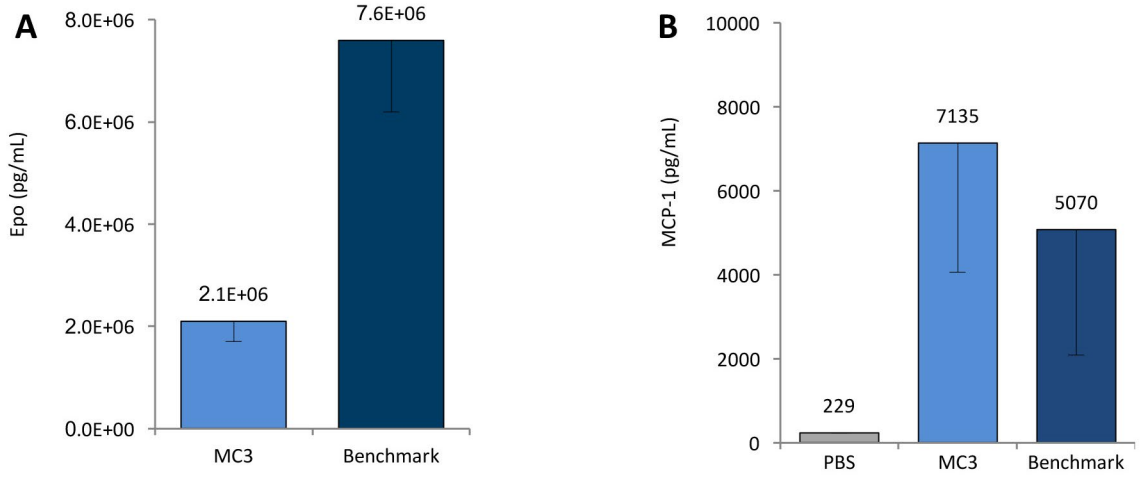


Figure 5. *Initial improvements in mRNA-LNP performance. Mice were administered Epo mRNA (0.5 mg/kg i.v.; n = 5) formulated either in an LNP composition analogous to the clinical patisiran formulation (MC3) or LNP 2 that incorporates formulation and process changes tailored toward mRNA payloads. Serum Epo (A) and cytokines represented by MCP-1 (B) were assessed at 4 h. Cytokine release at this dose was entirely attributable to the Epo mRNA that was crudely purified by standard silica spin columns.*

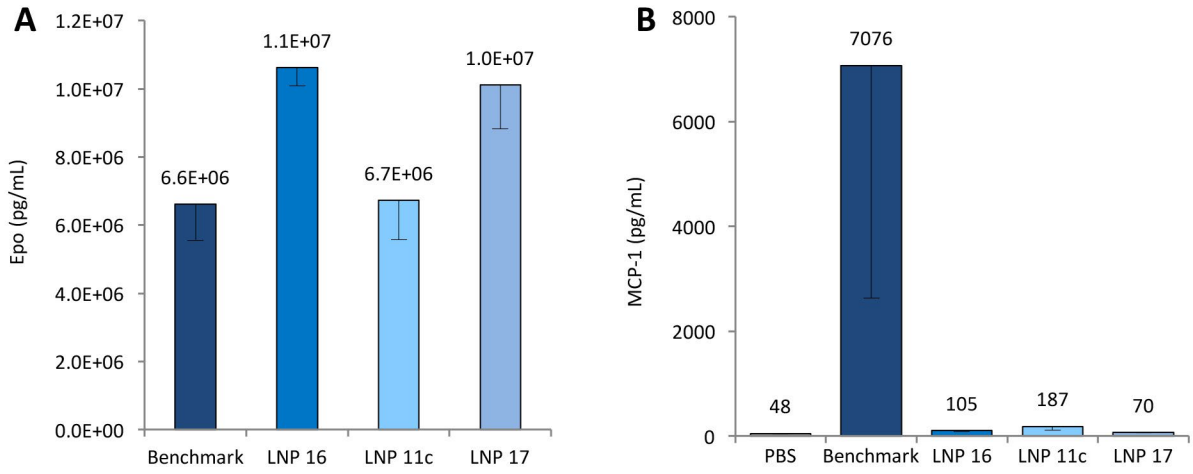


Figure 6. *Potency and cytokine response of novel mRNA-LNPs. Mice were administered silica gel purified Epo mRNA (0.5 mg/kg i.v.; n = 5) formulated either in LNP 2 or novel compositions LNP 16, LNP 11c, or LNP 17. Serum Epo (A) and cytokines represented by MCP-1 (B) were assessed at 4 h.*

continued

The induction of interferon response genes, such as IFIT1, in the target organ is known to be a far more sensitive measure of immune stimulation by nucleic acids than serum cytokine elevations. The use of novel LNP compositions greatly reduced the massive hepatic IFIT1 mRNA induction triggered by the silica gel purified mRNA; however, it is evident that the interferon response was still activated to some degree (Fig. 7). This unwanted and potentially harmful off-target effect of the mRNA is a function of RNA purity among other things; therefore, studies were repeated using high-quality HPLC-purified mRNA. The administration of a highly efficacious dose of HPLC-purified Epo mRNA (0.5 mg/kg) in the LNP 2 composition induced only low-level IFIT1 mRNA induction, and this interferon response was completely abrogated in the LNP 11 composition. These results confirm that the immune response at these efficacious doses is entirely attributable to the mRNA payload and demonstrates that LNP formulation design can be successfully applied to mRNA-LNPs to create mRNA drug product candidates with both high potency and minimal immune-stimulatory capacity.

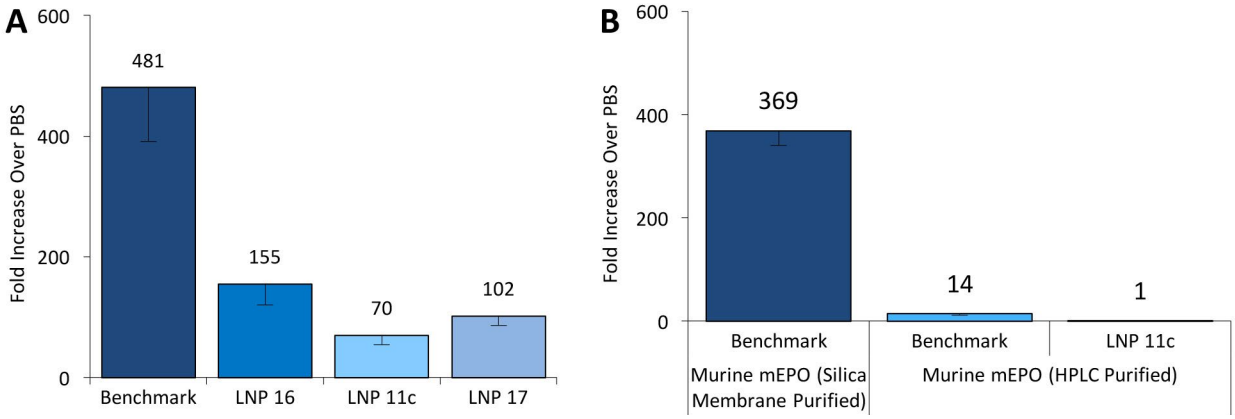


Figure 7. *Novel LNPs containing HPLC-purified mRNA caused minimal induction of the interferon (IFN) response. Mice were administered either silica gel (A) or HPLC purified (B) Epo mRNA (0.5 mg/kg i.v.; n = 5) formulated either in LNP 2 or novel compositions LNP 16, LNP 11c, or LNP 17. Hepatic IFIT1 mRNA levels were quantitated by branched DNA assay 4 h post-injection, normalized to GAPDH mRNA, and expressed as fold increase over saline-treated animals. HPLC purification significantly reduced induction of the IFN response (B), particularly in combination with novel LNP compositions such as LNP 11c.*

mRNA-based drugs have garnered increasing interest for a range of therapeutic strategies; however, their successful translation into the clinic demands appropriate attention. From our deep clinical experience we appreciate that the safe and successful translation of mRNA-LNP products into man requires careful attention to both potency and the capacity to activate undesirable immune responses. This is particularly true for mRNA payloads, which preclinical data suggest are more likely to provoke inflammatory responses than smaller oligonucleotides. Novel lipid compositions identified here are significantly more potent for mRNA delivery than those LNPs currently in the clinic. More importantly, their design avoids immune activation upon intravenous administration across a range of preclinical species and models. This novel approach to LNP design should greatly reduce the risk of IRRs and cytokine-mediated toxicities as these mRNA-LNP products enter in the clinic.

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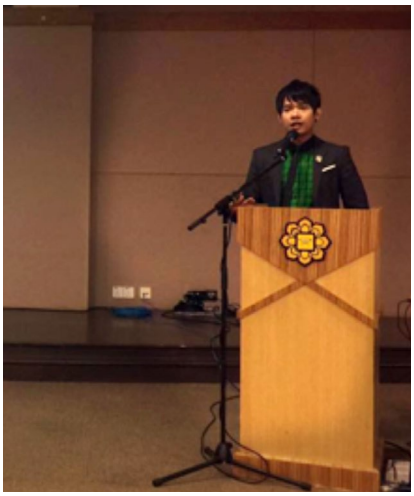
MyCRS Seminar 2017

Hazrina Abdul Hadi[1] and Mohd Cairul Iqbal Mohd Amin[2]

Realizing the importance of knowledge sharing in the world of pharmaceutical sciences, the Kulliyyah of Pharmacy, International Islamic University Malaysia (IIUM), aspires to provide a platform for the Malaysia Local Chapter of the Controlled Release Society (MyCRS) that brings pharmaceutical scientists from academia and industry together by organizing the MyCRS seminar series at IIUM.

This exciting one-day event took place at the banquet hall of the IIUM Kuantan Campus in Pahang, Malaysia, on April 6, 2017. The conference delegates were welcomed by the chairperson of the seminar, Hazrina Abdul Hadi, and MyCRS president Mohd Cairul Iqbal. The event was officiated by Juliana Mohd Jafri, the dean of the Kulliyyah of Pharmacy, IIUM.

Farahidah Mohamed sharing her thoughts with other participants.



Izzat Fahimuddin Mohamed Suffian presenting his work.

Fifty-five participants from local universities such as IIUM, Universiti Sains Islam Malaysia, International Medical University, Infrastructure University Kuala Lumpur, and University Technology MARA (UiTM) and industries (iKOP Sdn Bhd and Chulia Pharma Sdn. Bhd) attended this event.

Six speakers from four universities shared their knowledge and current research with all the attendees. The talks were divided into three categories: representatives from MyCRS, a session with young researchers, and a special guest via teleconference. The first talk started right after the opening ceremony, which was delivered by a representative from MyCRS, Prof. Cairul Iqbal (Universiti Kebangsaan Malaysia), followed by the young researcher session led by Izzat Fahimuddin Mohamed Suffian (IIUM). Farahidah Mohamed from IIUM also participated in this seminar as the third speaker. The afternoon session started with the young researcher session led by Awis Sukarni Mohd Sabree (IIUM), with Wong Tin Wui as the MyCRS representative from UiTM. Khuloud Al-Jamal (King's College London, U.K.) ended the seminar with her talk via teleconference on carbon nanotube uptake in the brain after intravenous injection in mice.

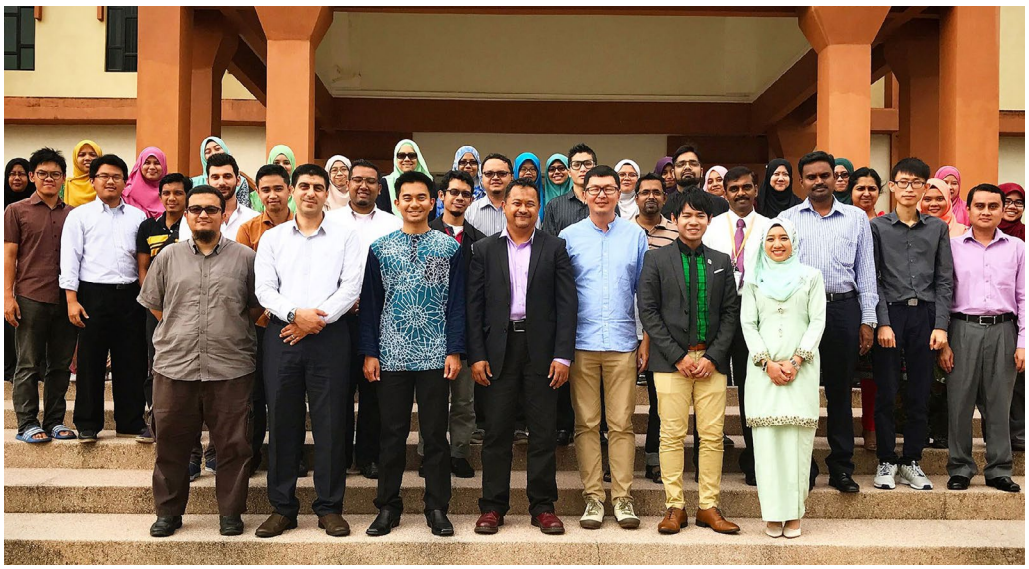


Photo session with all participants.

The seminar attendees found this event interesting and thought provoking. With the theme of "Cutting Edge Technologies in Pharmaceutical Sciences," the university and kulliyyah encourage MyCRS members and representatives to continue to move forward and embrace more challenges in coordinating more activities that will capture the true meaning and the importance of creating up-to-date pharmaceutical scientists in both academia and industry. ■

[1] International Islamic University of Malaysia.
[2] Universiti Kebangsaan Malaysia

First SPLC-CRS Young Scientist Meeting

João Nuno Moreira,[1] Dolores Torres,[2] Manuela Gaspar,[3] Maria José Blanco-Prieto,[4] and Manoli Igartua[5]

The first SPLC-CRS Young Scientist Meeting, an initiative of the Spanish-Portuguese Local Chapter of the Controlled Release Society (SPLC-CRS), took place in Santiago de Compostela, Spain, on April 23–24, 2017. This was a joint meeting with the TRANS-INT training workshop, from the TRANS-INT EU consortium led by Maria José Alonso from the University of Santiago de Compostela.

The meeting had strong support from the young members of SPLC-CRS. A total of 26 short communications were delivered, with a total of 49 participants.

The two best oral communications were selected by a committee formed by Caitriona O'Driscoll (University College Cork, Ireland), Carmen Alvarez (University of Santiago de Compostela), and David Brayden (University College Dublin, Ireland). The selected communications were:

- "Safer and More Predictable Therapies in Cell Encapsulation," by Ainhoa Gonzalez-Pujana, Faculty of Pharmacy, University of the Basque Country, Vitoria, Spain. This work has also been submitted for presentation at the 2017 CRS Annual Meeting & Exposition in Boston.

- "Biodistribution of Polymeric Nanocapsules: Engineering Particles for Lymph Node Targeting," by Ana Sara Cordeiro, Center for Research in Molecular Medicine and Chronic Diseases, University of Santiago de Compostela, Spain.

SPLC-CRS is glad to fund (with CRS support) the participation of Ainhoa Gonzalez-Pujana and Ana Sara Cordeiro at the 2017 Annual Meeting of the Controlled Release Society, taking place in Boston on July 16–19.

The winners and the members of the committee to select the best oral communications. Left to right: Caitriona O'Driscoll, Carmen Alvarez, Ainhoa Gonzalez-Pujana, Ana Sara Cordeiro, and David Brayden.

The first day of the meeting included the participation of Maria José Alonso and Justin Hanes from the CRS board, with the aim of disseminating the CRS mission among students and fostering their engagement with the society's activities.

On April 24, we had the opportunity to share the training workshop organized by the TRANS-INT EU consortium, in which two invited speakers participated: Justin Hanes (Johns Hopkins University School of Medicine, U.S.A.) and Felipe Casanueva (University Hospital Complex, University of Santiago de Compostela, Spain). The meeting ended with the TRANS-INT EU project award, won by Irene Santalices, a graduate student from University of Santiago de Compostela. ■

[1] University of Coimbra, Portugal.
[2] University of Santiago Compostela, Spain.
[3] University of Lisbon, Portugal.
[4] University of Navarra, Spain.
[5] University of the Basque Country, Spain.

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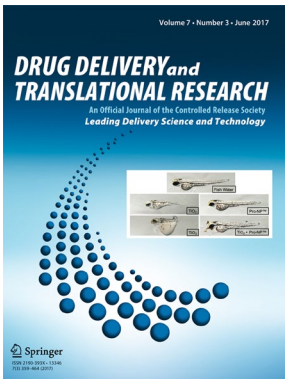
Drug Delivery and Translational Research Update

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

2016 *DDTR* Impact Factor = 3.094



DDTR's impact factor increased from 1.887 (2015) to 3.094 (2016). This is a remarkable 64% increase in impact factor after *DDTR* received its first impact factor in 2015. *DDTR*, an official journal of CRS and published by Springer-Nature, is currently ranked 80 of 256 titles in pharmacology and pharmacy (compared with 161/253 last year) and 41 of 128 titles in medicine, research, and experimental (compared with 78/124 last year). *DDTR* also surpassed 100,000 downloads in December 2016. *DDTR* has now received contributions from 45 countries, indicating a global reach and impact. Consider publishing your best translational drug delivery research in *DDTR* for greater visibility, and compete for the *DDTR* outstanding research paper award (www.controlledreleasesociety.org/about/Awards/Pages/DDTROustandingPaper.aspx). CRS members get free online access to the articles published in *DDTR* as a membership benefit.

Special Issues

DDTR has thus far published 16 special issues covering aspects of drug delivery in different disease conditions. Five more issues are under development. Consider developing a special issue for *DDTR* as a guest editor, which could be on a current topic of interest or based on symposia or conferences that you may be involved with. Please e-mail a proposal to me at labhasv@ccf.org for consideration. The upcoming issue is based on the CRS Canadian Local Chapter, to be edited by Michael Doschak of the University of Alberta (www.ualberta.ca/pharmacy/about-us/contact-us-and-people/people/michael-doschak), Emmanuel Ho of the University of Manitoba (http://umanitoba.ca/faculties/health_sciences/pharmacy/staff/ho.html), and Christine Allen of the University of Toronto (www.pharmacy.utoronto.ca/users/allencj).

Editor's Choice Publication

"An intravaginal ring that releases three antiviral agents and a contraceptive blocks SHIV-RT infection, reduces HSV-2 shedding, and suppresses hormonal cycling in rhesus macaques" by Derby *et al.* is an open access article (https://link.springer.com/article/10.1007/s13346-017-0389-0). Visit the *DDTR* website to read full articles.

Abstract: Women globally need access to multipurpose prevention technologies (MPTs) that prevent human immunodeficiency virus (HIV), sexually transmitted infections that increase HIV acquisition/transmission risk, and unintended pregnancy. Seeking an MPT with activity against HIV, herpes simplex virus-2 (HSV-2), and human papillomavirus (HPV), we developed a prototype intravaginal ring (IVR), the MZCL IVR, which released the antiviral agents MIV-150, zinc acetate, and carrageenan (MZC for short) and the contraceptive levonorgestrel (LNG). Previously, we showed that an MZC gel has potent activity against immunodeficiency viruses, HSV-2, and HPV and that the MZCL (MZC with LNG) IVR releases all four components in macaques *in vivo* at levels associated with efficacy. Vaginal fluid from treated macaques has *in vitro* activity against HIV, HSV-2, and HPV. Herein, we assessed the ability of the MZCL IVR to protect macaques against repeated co-challenge with HSV-2 and SHIV-RT (simian immunodeficiency virus [SIV] containing the reverse transcriptase gene from HIV) and prevent hormonal cycling. We evaluated *in vivo* drug release in co-challenged macaques by measuring drug levels in blood and vaginal fluid and residual drug levels in used IVRs. The MZCL IVR significantly prevented SHIV-RT infection, reduced HSV-2 vaginal shedding, and prevented cycling. No non-nucleoside HIV reverse transcriptase inhibitor (NNRTI)-resistant SHIV was detected in macaques that became infected after continuous exposure to MZC from the IVR. Macaques wearing the MZCL IVR also had carrageenan levels in vaginal fluid expected to protect from HPV (extrapolated from mice) and LNG levels in blood associated with contraceptive efficacy. The MZCL IVR is a promising MPT candidate that warrants further development. ■

People in the News

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

Nemaura Pharma Appoints Dr. Werner Wessling as Director of Strategic Alliances

Business Wire: April 7, 2017 – LOUGHBOROUGH, England – U.K. biotech company Nemaura Pharma is continuing its growth plans with the appointment of leading global pharmaceutical expert Dr. Werner Wessling. Dr. Wessling will join the management team as director of strategic alliances with a remit to expand Nemaura's commercial partnerships and collaborations in drug formulation and medical device technologies globally.

Dr. Wessling is a highly respected deal-maker and negotiator in pharmaceutical product development, licensing, and commercialization. His early career in management with Beiersdorf AG and Altana AG subsequently led to his appointment in 1987 as VP business development worldwide for LTS Lohmann Therapie-Systeme, the world's largest transdermal patch manufacturer. Dr. Wessling subsequently built a successful commercial career with LTS, helping to grow the global pharmaceutical company to become the world's largest transdermal patch manufacturer with 1,300 employees. He was appointed senior VP corporate development in 2000, a position he held until 2016. During that period, Dr. Wessling was a board delegate LTS Lohmann Therapy-Systems Inc. N.J., U.S.A. (1994-2016), managing director CRS GmbH (2006-14) and managing director IIS GmbH (2011-16) – both subsidiaries of LTS.

Nemaura CEO Dr. Faz Chowdhury said: "We highly value Dr. Wessling's expertise and strategic industry insight built over 30 years with LTS, and his extensive network will support our ambitious plans for expansion and growth. Our work is already poised to transform the way therapeutic drugs are administered through the skin using our advanced delivery systems, and Dr. Wessling's arrival will further accelerate our impact as a major global player."

During his tenure with LTS Lohmann Therapie-Systeme, Dr. Werner Wessling was responsible for multiple licensing and patents negotiations, and for closing deals in Europe, North America, and Asia (Japan and Korea). Most of the innovative and profitable products in the current LTS portfolio are a result of Dr. Wessling's skilful negotiation and partnering efforts and have generated more than $10 billion in lifetime marketing partner revenues.

Dr. Wessling commented: "I have accepted the opportunity to work with Dr. Chowdhury because I believe Nemaura's technologies will be able to solve some of the issues in the effective delivery of biologics and vaccines. Nemaura's growth since start-up in 2005 has been impressive. It shows what can be achieved when you build a high-calibre team committed to innovation and to improving patient lifestyle and quality of life."

The value of the global skin drug delivery market is expected to reach £33 billion by 2018 and Nemaura aims to be one of the leading pharmaceutical technologists in this market.

Founded in 2005, Nemaura Pharma is a private specialist biotech company with headquarters and research facilities in the Advanced Technology Centre on the Loughborough University Science and Enterprise Park (LUSEP) in the United Kingdom.

The company employs multi-disciplinary teams of scientists and engineers working in cutting edge innovative drug formulation and medical device technologies designed to radically improve the way drugs are administered through the skin. It has patents secured or pending in multiple countries across numerous patent families.

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

Companies in the News

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

May

Ocular Therapeutix™ Presented Phase 3 Data for DEXTENZA™ at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting

Business Wire: May 11, 2017 – BEDFORD, MA, U.S.A. – Ocular Therapeutix, Inc. (NASDAQ: OCUL), a biopharmaceutical company focused on the development, manufacturing, and commercialization of innovative therapies for diseases and conditions of the eye, presented ocular pain data from a pooled analysis from three phase 3 clinical trials evaluating the efficacy and safety of DEXTENZA (dexamethasone insert) 0.4 mg for intracanalicular use, for the treatment of ocular pain and inflammation following cataract surgery, at the Association for Research in Vision and Ophthalmology (ARVO) annual meeting in Baltimore, MD.

The U.S. Food and Drug Administration (FDA) has set a target action date under the Prescription Drug User Fee Act (PDUFA) of July 19, 2017, for a decision regarding the potential approval of DEXTENZA. The upcoming PDUFA date is for a new drug application (NDA) for the treatment of ocular pain following ophthalmic surgery based on a phase 2 study and two phase 3 trials. The third and most recent phase 3 study results are not currently being evaluated by FDA as part of the current NDA.

The pooled analysis includes data from all three phase 3 trials, in which 79% of DEXTENZA patients reported no pain at day 8 compared with 56.9% of the placebo patients. Across all three phase 3 trials, a greater proportion of placebo patients experienced at least one ocular adverse event (AE) as compared with DEXTENZA patients. The most frequent ocular AEs were anterior chamber inflammation, increased intraocular pressure, corneal edema, and eye inflammation. There were no treatment-related serious adverse events (SAEs) in either group.

"The pooled safety and efficacy profile suggests that DEXTENZA may offer an alternative to current post-operative steroid eye drops, which are associated with compliance issues," said Jonathan H. Talamo, MD, chief medical officer of Ocular Therapeutix. "If approved, DEXTENZA has the potential to reduce the burden of administering topical eye drops following ophthalmic surgery, and to enhance patient and provider experience by enabling physicians to control the entire course of steroid therapy with a single insertion."

A poster describing the results of the pooled analysis from three phase 3 clinical trials evaluating the efficacy and safety of DEXTENZA was presented at the ARVO annual meeting:

"DEXTENZA™ (dexamethasone insert) 0.4 mg vs. Placebo for the Treatment of Ocular Pain after Cataract Surgery: Results of Three Phase 3 Studies" – Posterboard #B0159, Abstract #1826-B0159

Three phase 3 trials were pooled to evaluate the integrated efficacy of DEXTENZA when placed in the canaliculus of the eye for the treatment of post-surgical pain in subjects who have undergone cataract extraction with intraocular lens implantation. The pooled analysis confirmed the results of the individual phase 3 trials. DEXTENZA, compared with placebo vehicle insert, resulted in a significantly greater proportion of patients who reported an absence of ocular pain following cataract surgery.

The company also presented other data at the ARVO annual meeting including:

- Plasma pharmacokinetics of DEXTENZA in healthy volunteers
- The evaluation of a phase 2b study for OTX-TP, the company's sustained release travoprost intracanalicular insert for the treatment of glaucoma and ocular hypertension compared to timolol drops
- Preclinical data on tolerability and pharmacokinetics of a 6 month sustained release hydrogel TKI depot for tyrosine kinase inhibitors (TKIs)
- Efficacy of a 6 month sustained release hydrogel TKI depot in a VEGF-induced retinal leakage model
- Outcomes in cataract surgery using ReSure® Sealant for the intraoperative management of clear corneal incisions

DEXTENZA has been studied in three phase 3 trials. All trials were prospective, multicenter, parallel-arm, double-masked, and vehicle-controlled to evaluate the safety and efficacy of DEXTENZA for the treatment of ocular pain and inflammation following

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cataract surgery. In two trials, patients were randomized 2:1 (DEXTENZA to placebo vehicle insert); while the in the most recent study patients were randomized 1:1. A total of 926 patients were enrolled (*n* = 541, DEXTENZA; *n* = 385, placebo vehicle insert) who were undergoing clear corneal cataract surgery. Immediately following surgery, patients were randomized to insertion of either DEXTENZA or a placebo insert. Primary efficacy endpoints evaluated the differences between the DEXTENZA treatment group and the placebo group for the absence of anterior chamber cells at day 14 and absence of pain at day 8. Secondary efficacy endpoints included absence of anterior chamber cells, absence of ocular flare, and absence of ocular pain across relevant time points during the 30-day treatment period.

DEXTENZA is placed through the punctum, a natural opening in the eye lid, into the canaliculus and is designed to deliver dexamethasone to the ocular surface for up to 30 days. Following treatment, DEXTENZA resorbs and exits the nasolacrimal system without need for removal.

In January, Ocular Therapeutix resubmitted an NDA to the FDA for DEXTENZA for the treatment of ocular pain following ophthalmic surgery. The FDA has set a PDUFA target action date of July 19, 2017. Subject to the approval of the NDA for post-surgical ocular pain by the FDA, Ocular Therapeutix intends to submit a supplement to its NDA for DEXTENZA to broaden its label to include a post-surgical ocular inflammation indication, based on the results of the third phase 3 study.

Ocular pain and inflammation are common side effects following ophthalmic surgery. Physicians prescribe topical corticosteroids as part of the standard of post-operative care. If left untreated, inflammation of the eye may result in further ocular complications, which in some cases may cause permanent loss of vision. According to U.S. Census data, by the year 2020 it is estimated that the number of Americans diagnosed with cataracts will rise to approximately 30 million, representing a 32% increase over current prevalence estimates.

According to Market Scope, approximately 3.9 million cataract cases and over 5.6 million ocular surgeries were performed in the United States in 2016.

Ironwood Pharmaceuticals Presents Data Further Elucidating Linaclotide's Effect on Pain at Digestive Disease Week® 2017

Business Wire: May 9, 2017 – CAMBRIDGE, MA, U.S.A. – Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD), a commercial biotechnology company, this week presented clinical data on the effect of linaclotide on abdominal pain in irritable bowel syndrome with constipation (IBS-C) patients and preclinical data on linaclotide's effect on pain originating in other visceral organs at Digestive Disease Week® (DDW) 2017 in Chicago.

Detailed data from a phase IIb clinical trial evaluating the effects of two investigational delayed release formulations of linaclotide on abdominal pain in adult patients with IBS-C were presented as a late-breaker by Dr. William Chey, University of Michigan. Ironwood previously reported positive topline data for both delayed release formulations in December 2016. In addition, Ironwood and its collaborators delivered oral and poster presentations at DDW regarding a series of preclinical studies suggesting that linaclotide may have effects on pain associated with conditions affecting visceral organs outside of the gastrointestinal tract, such as the bladder or vagina.

"Millions of patients are estimated to suffer from chronic conditions characterized by pain in the abdominal and pelvic regions, and pain is a primary symptom driving patients to seek treatment from a healthcare provider," said Mark Currie, Ph.D., chief scientific officer and president of research and development at Ironwood. "As we continue to better understand linaclotide's effect on visceral hypersensitivity, we look forward to further studying its ability to relieve pain in IBS-C, as well as potentially in other conditions such as IBS with diarrhea, IBS-mixed, ulcerative colitis, diverticulitis, interstitial cystitis/bladder pain syndrome, and endometriosis."

In the late-breaking clinical science session at DDW, Dr. Chey presented data (poster presentation Tu2031) from a double-blind, placebo-controlled, dose-ranging phase IIb trial evaluating two investigational delayed release formulations of linaclotide in adult patients with IBS-C.

Data from the phase IIb study of linaclotide delayed release-1 (DR1) demonstrated dose-dependent improvements in abdominal pain as well as in complete spontaneous bowel movements and stool consistency, compared to placebo, across all studied doses. Additionally, improvements in abdominal pain and stool consistency were greater for the DR1 300 mcg dose compared to the 290 mcg immediate release (IR) formulation of linaclotide. Data from the phase IIb study of linaclotide delayed release-2 (DR2) showed that all studied doses improved abdominal pain and other abdominal symptoms, relative to placebo, with no apparent effect on bowel movement

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function, as intended. These comparisons reflect numerical differences. Diarrhea was the most common adverse event. Across all DR1 and DR2 dose groups, 0–3% of patients withdrew from the trial due to diarrhea.

"The data from the linaclotide delayed release study represent a significant advance in the GI field and in our understanding of abdominal pain," said Dr. Chey. "The DR1 data suggest that delaying delivery of linaclotide to the mid-ileum region of the distal small intestine and colon could improve abdominal pain relief while preserving constipation relief. The DR2 data are also exciting: delaying linaclotide delivery to the ileocecal junction in the colon could improve abdominal pain relief with little to no effect on fluid secretion, which could represent a potential opportunity to treat patients suffering from lower gastrointestinal conditions characterized by abdominal pain."

Ironwood and its U.S. collaboration partner Allergan intend to engage with the U.S. Food and Drug Administration (FDA) to discuss phase III development plans, with trials in adults with IBS-C expected to begin in the second half of 2017. The companies are evaluating DR2 in adult patients with non-constipation subtypes of IBS, and plan to discuss next steps with the FDA for advancing DR2 into phase IIb dose-ranging clinical trials.

In a poster presentation titled "Linaclotide Attenuates Visceral Organ Crosstalk: Importance of Guanylate Cyclase C (GC-C) Activation in Reversing Colonic Hypersensitivity Induced by Urinary Bladder Hyperpermeability" (poster presentation Tu1602), Ehsan Mohammadi, University of Oklahoma Health Science Center, presented preclinical data in a model of colonic hypersensitivity induced by bladder injury, which suggested that oral administration of linaclotide significantly reduced this colonic hypersensitivity, as measured by visceromotor responses (abdominal contractions) to colonic distention and pERK expression (spinal nerve activation). These data suggest that GC-C agonism may be able to affect various abdominal and pelvic area organ pain through visceral organ crosstalk, which is enabled by the fact that multiple organs in this region of the body share sensory peripheral and central innervation pathways.

Just as visceral organ cross-sensitization is hypothesized to explain linaclotide's ability to reduce colonic sensitivity caused by bladder injury, a study by Pei Ge, Ironwood Pharmaceuticals, tested the hypothesis that linaclotide could reduce visceral pain in other pelvic conditions. In a poster presentation titled "Oral Administration of the Gut-Restricted Guanylate Cyclase-C Agonist, Linaclotide, Reduces Endometriosis-Induced Vaginal Hyperalgesia" (poster presentation Mo1541), both acute and chronic oral administration of linaclotide significantly reduced vaginal pain in a preclinical model of endometriosis, measured by visceromotor responses to vaginal distension. GC-C expression was detected in the intestine, but not in endometrial cysts and the vagina, suggesting that the effect of linaclotide on visceral pain in this model involves shared nervous pathways between visceral organs.

An oral presentation delivered by Stuart Brierley, Ph.D., SAHMRI, Flinders University, Adelaide, SA, Australia, titled "Chronic Oral Administration of Linaclotide Inhibits Nociceptive Signaling in Response to Noxious Colorectal Distension in a Model of Chronic Visceral Hypersensitivity" (oral presentation 1098), the results of a preclinical study evaluating the effects of chronic oral administration of linaclotide on colonic hypersensitivity caused by colorectal distention were shown. In this study, linaclotide reduced colonic hypersensitivity, as measured by visceromotor responses, and also reversed the sprouting of colonic afferent nerves in the spinal cord, which had sprouted in response to pain stimuli in preclinical models. These data suggest that further study is warranted looking into whether linaclotide has the ability to reduce hypersensitivity in the colon and reverse neuroplasticity within the spinal cord associated with chronic visceral hypersensitivity.

Another preclinical study by Dr. Brierley provided additional insight on the mechanism of GC-C agonism in pain reduction by investigating its effects on pain-sensing nerves in the dorsal root ganglia (DRG). In an oral presentation titled "Extracellular cGMP Reduces the Excitability of Sensory Dorsal Root Ganglion Neurons via an Extracellular Mechanism" (oral presentation 723), he showed that, in this preclinical study, linaclotide did not directly inhibit DRG neurons, but rather its downstream mediator, cyclic guanosine monophosphate (cGMP), was responsible for decreasing activity of these pain-sensing nerves. The study also showed that extracellular cGMP did not enter DRG neurons, lending further support to the hypothesis that cGMP's inhibitory effect is mediated via an extracellular, rather than intracellular, mechanism.

Linaclotide is a guanylate cyclase-C (GC-C) agonist that binds to the GC-C receptor locally, within the intestinal epithelium, and is thought to work in two ways, based on nonclinical studies. Activation of GC-C results in increased intestinal fluid secretion and accelerated transit, as well as a decrease in the activity of pain-sensing nerves in the intestine. The clinical relevance of the effect on pain fibers, which is based on nonclinical studies, has not been established. Linaclotide is marketed by Ironwood and Allergan plc in the United States as LINZESS® and is indicated for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC), with nearly 1.5 million unique patients in the United States having filled nearly 7.5 million linaclotide prescriptions since launch, according to QuintilesIMS. In Europe, Allergan markets linaclotide under the brand name

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CONSTELLA® for the treatment of adults with moderate to severe IBS-C. In Japan, Ironwood's partner Astellas markets linaclotide under the brand name LINZESS for the treatment of adults with IBS-C. Ironwood also has partnered with AstraZeneca for development and commercialization of linaclotide in China and with Allergan for development and commercialization of linaclotide in all other territories worldwide.

OptiNose Raises $37 Million in Series D Funding Led by Fidelity

Business Wire: May 9, 2017 – YARDLEY, PA, U.S.A. – OptiNose, a commercial-stage ENT/allergy specialty pharmaceutical company, today announced that it has closed a $37 million series D financing led by Fidelity Management and Research Company with participation from Avista Capital Partners, Entrepreneurs Fund, and other current investors. OptiNose will use the additional capital to fund commercial readiness for the launch of its lead product candidate, OPN-375, in the United States.

"We are building a company dedicated to meeting the needs of patients treated by ENT/allergy specialists and using our patented technology and other approaches to create innovative products that improve clinical outcomes and make lives better," said Peter Miller, CEO of OptiNose. "Chronic rhinosinusitis (CRS) with or without nasal polyps, our current focus, is a large market worldwide. Data suggest there is tremendous dissatisfaction with the current medical treatment options."

OptiNose's first technology is based on a patented closed-palate Breath Powered® platform that is used to develop unique new exhalation delivery systems (EDS) capable of high and deep intranasal deposition of medication. When combined with carefully selected molecules, the EDS approach enables creation of novel pharmaceutical products with potential for meaningful new clinical benefits. OptiNose's lead product candidate, OPN-375, is an EDS with fluticasone propionate and is being developed for treatment of nasal diseases characterized by chronic inflammation deep in the nose, such as nasal polyposis and chronic sinusitis.

A new drug application (NDA) seeking marketing approval for the treatment of nasal polyposis was submitted to the U.S. Food and Drug Administration (FDA) in November 2016, and the Prescription Drug User Fee Act (PDUFA) goal date, the target date for the FDA to complete its review of the NDA, is in September 2017.

"This is a serious disease, and it causes a high degree of suffering for millions of people in the U.S. alone. OPN-375 could fill an important role in the care pathway for the many patients who do not get satisfactory relief with current treatments," stated Ramy Mahmoud, president and COO of OptiNose. "We have an excellent team that is eager to make this product available to patients, and this latest round of funding will put us in a position to make the investments needed to ensure that, if approved, we are ready for launch in the first half of 2018."

OptiNose is a commercial stage ENT/allergy specialty pharmaceutical company on a mission to improve lives. The company's first technology involves a patented closed-palate Breath Powered® platform used to develop proprietary exhalation delivery systems (EDS) capable of high and deep intranasal deposition of medication. These exhalation delivery systems enable creation of products with the potential for meaningful new clinical benefits. OptiNose successfully developed and out-licensed its first product at the end of phase 3 development, Onzetra® Xsail® (sumatriptan nasal powder), to Avanir Pharmaceuticals (since acquired by Otsuka Pharmaceutical Co., Ltd.). Onzetra Xsail received FDA approval and was launched in the U.S. in 2016. The company's second product and current lead product candidate, OPN-375, is an EDS with fluticasone propionate and is being developed for treatment of nasal diseases characterized by chronic inflammation such as nasal polyposis and chronic sinusitis. An NDA seeking marketing approval for the treatment of nasal polyposis was submitted to the FDA in November 2016, and the Prescription Drug User Fee Act (PDUFA) goal date is in September 2017. Subsequent OptiNose pipeline products will aim to serve the needs of patients treated by ENT and allergy specialists and are expected to include those using EDS and other technologies. The company is also currently engaged in the early development of products for neurologic orphan diseases where the "nose-to-brain" application of an EDS may enable improved treatment. This includes OPN-300 (Prader-Willi syndrome, autism, others) and OPN-21 (narcolepsy and others). OptiNose has corporate offices in the U.S., U.K., and Norway.

Novaliq Conducts a First-in-Class Ocular Neuropathic Pain and Anti-Inflammatory Cannabinoid Drug Development Program in Collaboration with the University of Cologne, Germany

Business Wire: May 8, 2017 – HEIDELBERG, Germany – Novaliq GmbH, a specialty pharmaceutical company with a disruptive drug delivery platform that transforms poorly soluble drugs into effective therapeutics for ophthalmology, today announced successful application of a first-in-class ocular neuropathic pain and anti-inflammatory cannabinoid-based dry eye disease (DED) treatment approach in collaboration with the University of Cologne, Germany.

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DED is one of the most common eye pathologies, with neuropathic ocular pain a frequent underserved condition of this disease. The novel therapeutic approach has been proof-tested in a consecutive research program (Nov-07) that explores the development of new dry eye therapies targeting the cannabinoid receptor system using Novaliq's proprietary EyeSol® drug delivery technology. Well-known for its neuroprotective and pain-inhibiting properties, various molecules targeting these receptors are extremely unstable in water-based formulations and undergo fast autoxidation, which makes the development of cannabinoid receptor targeting eye drops challenging. It is believed that applying EyeSol® technology to these molecules will result in enhancing its topical bioavailability, stability, and efficacy.

"Increasing evidence is available on the importance of neuropathic ocular pain in DED. Based on solid results of our ongoing test series, we expect a significant impact of Novaliq's first-in class Nov-07 program in comparison with existing DED drugs on an established DED mouse model," said Professor Philipp Steven, MD, principle investigator, Ocular Surface Group at the Department of Ophthalmology, University of Cologne, Germany. "We are now translating evidence from our experimental model into final, conformational studies in close cooperation with Novaliq for a phase I clinical study in the near future. Based on the preclinical results, we believe that the Nov-07 program will facilitate the treatment of DED utilizing a dual mode of action towards inflammation and ocular neuropathic pain."

"We are very excited to work in partnership with Professor Steven and his team at the University of Cologne," said Sonja Krösser, Ph.D., vice president of preclinical and clinical development, Novaliq. "We anticipate that this new area of research in DED will further highlight the importance and awareness of inflammation and ocular neuropathic pain in dry eye. Offering an effective treatment for dry eye patients associated with symptomatic ocular neuropathic pain will be a milestone in the treatment of DED."

Christian Roesky, Ph.D., managing director and CEO, Novaliq added, "With this program we demonstrate the power of EyeSol® as an enabling technology for developing truly differentiated drugs with the ability to transform ocular therapeutics by overcoming the current limitations of water in eye care."

Novaliq GmbH, founded in 2007, is a Heidelberg based specialty pharmaceutical company focused on ophthalmology. Its mission is to transform poorly soluble drugs into effective ocular therapeutics for both the front and the back of the eye. Novaliq's proprietary EyeSol® technology enhances the topical bio availability, 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 has developed a tiered and long-term sustainable dry eye family of truly differentiated products that addresses the different needs of dry eye patients. Novaliq's most advanced product is NovaTears® with CE-approval marketed under the brand name EvoTears® in Europe. CyclASol®, a second generation prescription drug, is currently in preparation for a pivotal trial. More on www.novaliq.com.

Glaukos Completes Patient Enrollment in Phase II Clinical Trial for iDose™ Travoprost Intraocular Implant in Glaucoma Patients

Business Wire: May 3, 2017 – SAN CLEMENTE, CA, U.S.A. – Glaukos Corporation (NYSE: GKOS), an ophthalmic medical technology company focused on the development and commercialization of breakthrough products and procedures designed to transform the treatment of glaucoma, today announced the completion of patient enrollment in the U.S. investigational new drug (IND) phase II study of its Travoprost intraocular implant with the iDose™ delivery system in patients with glaucoma.

Implanted during a micro-invasive procedure, the iDose is designed to continuously elute therapeutic levels of medication from within the eye for extended periods of time. It is filled with a special formulation of travoprost, a prostaglandin analog used to reduce elevated intraocular pressure, and capped with a membrane designed for continuous controlled drug elution into the anterior chamber. When depleted, the implant can be removed and replaced in a similar, subsequent micro-invasive procedure.

The 150-patient, multi-center, randomized, double-blind phase II trial will evaluate two models of the iDose delivery system with different travoprost elution rates compared to a topical timolol maleate ophthalmic solution, 0.5%. The trial, which will assess preliminary safety and efficacy in lowering intraocular pressure in patients with open-angle glaucoma, will be unmasked after 12 weeks of follow-up, with a topline readout expected later in 2017. Results of the phase II trial are expected to form the basis for the company's submission to the FDA to conduct expanded phase III trials on the iDose delivery system.

"Our completion of patient enrollment in the iDose phase II trial means that we have achieved an important and timely milestone in our goal to provide glaucoma patients and their physicians a comprehensive set of micro-scale devices and drug-delivery systems that address a full range of glaucoma disease state progression," said Thomas Burns, Glaukos president and chief executive officer. "We believe that the iDose delivery system has the potential to overcome many of the drawbacks associated with topical glaucoma

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medications. We look forward to these initial trial results and to moving towards commencement of phase III clinical trials to determine the longer-term efficacy of our novel iDose delivery system."

Glaukos designed the iDose to be an alternative to chronic, daily prescription eye drop therapy, which is subject to high rates of patient non-compliance and may cause long-term ocular surface irritation or damage in glaucomatous eyes. The titanium implant is comparable in size to the company's proprietary Micro-Invasive Glaucoma Surgery (MIGS) devices.

Glaucoma is characterized by progressive, irreversible, and largely asymptomatic vision loss caused by optic nerve damage. There is no cure for the disease and reducing intraocular pressure is the only proven treatment. According to Market Scope, more than 80 million people worldwide have glaucoma, including 4.5 million people in the United States. Open-angle glaucoma is the most common form, affecting approximately 3.6 million people in the United States.

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

Xenetic Biosciences Presents Case Study of PolyXen™ Platform Technology at the 13th Annual Protein Engineering Summit (PEGS) Boston

Business Wire: May 1, 2017 – LEXINGTON, MA, U.S.A. – Xenetic Biosciences, Inc. (NASDAQ: XBIO) ("Xenetic" or the "company"), a clinical-stage biopharmaceutical company focused on the discovery, research, and development of next-generation biologic drugs and novel orphan oncology therapeutics, announced today that it is presenting a case study highlighting the company's proprietary drug development platform technology, PolyXen™, at the 13th Annual PEGS Boston conference being held May 1–5, 2017 in Boston, MA.

The abstract titled, "Polysialylation – A Platform Technology for Enhancing Therapeutic Proteins and Its Clinical Application," is being presented in a scientific poster presentation as a part of "Poster Session A" on May 1–2, 2017. Curtis A. Lockshin, Ph.D., chief scientific officer of Xenetic, will also present results from the case study in an oral presentation on Tuesday, May 2, 2017 at 9:00 AM EDT as part of the Conquering Disease session of the Fusion Protein Therapeutics track of the Bioconjugates stream.

PolyXen is Xenetic's platform technology designed to improve the half-life and other pharmacological properties of biologic drugs, in which polysialic acid ("PSA"), a naturally occurring, hydrophilic, non-immunogenic, linear homopolymer of sialic acid (colominic acid), is attached to a protein to improve its *in vivo* pharmacokinetics and pharmacodynamics.

The positive data from the case study showed that the attachment of PSA ("polysialylation") led to retained or only slightly decreased biological activity, improved stability against proteases and thermal stress, and significantly prolonged circulating half-life. For example, the half-life of polysialylated erythropoietin ("PSA-EPO", "ErepoXen™") = ~400 hours in patients with chronic kidney disease ("CKD") after subcutaneous administration, versus the half-life of rhEPO = ~22 hours.

The company's PolyXen delivery technology has been clinically validated in phase 1 and phase 2 studies, where ErepoXen was shown to be efficacious at correcting and maintaining hemoglobin levels, while being well tolerated in humans, and without eliciting immune response after repeated dosing. ErepoXen is currently in ongoing phase 2/3 clinical development through the company's partners and shareholders, the Serum Institute of India and SynBio of Russia, for the treatment of anemia in CKD patients.

The phase 1 and phase 2 clinical trials of ErepoXen in CKD patients not on dialysis, highlighted its significantly improved pharmacokinetic properties and non-immunogenicity, suggesting that PSA-EPO has commercial potential as a next-generation long-acting ESA for managing anemia. The PolyXen polysialylation platform has been expanded to improve other therapeutic proteins, including PSA-FVIII, which is currently being evaluated in a phase 1/2 clinical trial for the treatment of hemophilia A with Xenetic's partner, Shire plc (LSE: SHP, NASDAQ: SHPG).

"We continue to establish a growing body of data demonstrating the broad utility of Xenetic's proprietary PolyXen platform technology for the creation of next-generation protein therapeutics, which confers the same benefits without many of the

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shortcomings which exist in the current therapies," commented Dr. Lockshin. "These significant, pharmacologically important attributes such as biodegradability, protease protection, enhanced thermal stability, immune system shielding, and half-life extension make the addition of polysialic acid to therapeutics a clear advantage over other technologies."

The poster being presented at the 13th Annual PEGS Boston will be accessible on the publications page of the company's website, www.xeneticbio.com, following the conference.

PolyXen is a patent-protected platform technology for creating proprietary, next-generation protein therapeutics by attaching polysialic acid ("PSA"), a biodegradable polymer found in living systems, to existing protein or peptide therapeutics, which can improve their pharmacological properties.

Attachment of PSA ("polysialylation") to a therapeutic increases its apparent size, which reduces systemic clearance rates, while shielding the protein from other degradation pathways. The PolyXen platform permits optimization of a target therapeutic's pharmacological properties, by controlling the amount, size, and sites of attachment of the PSA polymers.

In clinical and preclinical settings, therapeutic proteins polysialylated with the PolyXen platform have been shown to have extended circulating half-life, improved thermodynamic stability, and resistance to proteases, while retaining pharmacological activity. Numerous human clinical trials to date have shown no evidence of PSA-induced immunogenicity.

Xenetic Biosciences, Inc. is a clinical-stage biopharmaceutical company focused on the discovery, research, and development of next-generation biologic drugs and novel orphan oncology therapeutics. Xenetic's proprietary drug development platforms include PolyXen™, which enables next generation biologic drugs by improving their half-life and other pharmacological properties. Xenetic's lead investigational product candidates include oncology therapeutic XBIO-101 (sodium cridanimod) for the treatment of progesterone resistant endometrial cancer (EC), and a polysialylated form of erythropoietin for the treatment of anemia in pre-dialysis patients with chronic kidney disease.

Xenetic is also working together with Shire plc (formerly Baxalta, Baxter Incorporated, and Baxter Healthcare) to develop a novel series of polysialylated blood coagulation factors, including a next generation Factor VIII. This collaboration relies on Xenetic's PolyXen technology to conjugate polysialic acid ("PSA") to therapeutic blood-clotting factors, with the goal of improving the pharmacokinetic profile and extending the active life of these biologic molecules. Shire is a significant stockholder of the company, having invested $10 million in the company during 2014. The agreement is an exclusive research, development, and license agreement that grants Shire a worldwide, exclusive, royalty-bearing license to Xenetic's PSA patented and proprietary technology in combination with Shire's proprietary molecules designed for the treatment of blood and bleeding disorders. Under the agreement, Xenetic may receive regulatory and sales target payments for total potential milestone receipts of up to $100 million plus royalties on sales. Additionally, Xenetic has previously received strategic investments from OPKO Health (Nasdaq: OPK), Serum Institute of India Limited, and Pharmsynthez.

Xenetic is also developing a broad pipeline of clinical candidates for next generation biologics and novel oncology therapeutics in a number of orphan disease indications. For more information, please visit the company's website at www.xeneticbio.com.

Kala Pharmaceuticals Announces Positive Results from Confirmatory Phase 3 Trial of KPI-121 1% Following Cataract Surgery

Business Wire: May 1, 2017 – WALTHAM, MA, U.S.A. – Kala Pharmaceuticals, Inc. (Kala), a developer of innovative ophthalmic medicines based on its proprietary mucus-penetrating particle (MPP) technology, today announced positive top-line results from its confirmatory phase 3 trial of KPI-121 1% for the treatment of inflammation and pain in patients who have undergone cataract surgery. KPI-121 1% dosed twice-a-day for two weeks achieved statistical significance versus placebo for both primary efficacy endpoints and all secondary endpoints. KPI-121 1% was well tolerated with no significant treatment-related safety findings observed during the trial. These positive trial results are a follow on to Kala's first phase 3 trial for KPI-121 1% following cataract surgery that also achieved statistical significance for both primary endpoints with twice-a-day dosing.

"The significant improvement in the treatment of inflammation and pain with twice-a-day dosing of KPI-121 in this trial builds on the success of our first phase 3 trial in cataract surgery," said Kim Brazzell, Ph.D., chief medical officer of Kala. "We believe KPI-121 represents an important, near-term product opportunity for Kala as the first twice-a-day dosed steroid product for patients with post-operative inflammation and pain following ocular surgery. Based on the success of this trial, our plan is to submit a new drug application to the FDA for KPI-121 1% for the treatment of post-operative inflammation and pain following ocular surgery in late 2017."

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The phase 3 multi-center, randomized, double-masked, placebo-controlled, parallel-group trial in 520 patients was designed to evaluate the efficacy and safety of KPI-121 1% ophthalmic suspension dosed twice-a-day, versus placebo, in patients who experienced anterior ocular inflammation following cataract surgery. Patients were randomized to receive either KPI-121 1% or corresponding placebo, and both were administered twice-a-day for two weeks, with evaluations at days four, eight, and 15. The primary efficacy endpoints were the proportion of patients with complete resolution of anterior chamber cells (a marker of ocular inflammation) in the study eye at day eight, and the proportion of subjects with Grade 0 pain in the study eye at day eight.

Statistically significant differences favoring KPI-121 1% administered twice-a-day versus placebo were achieved for both primary endpoints, the proportion of patients with complete resolution of anterior chamber cells at day 8 ($P = 0.01$), and proportion of patients with complete resolution of ocular pain at day 8 ($P < 0.0001$). Statistical significance was also achieved for all predefined secondary endpoints (complete resolution of anterior chamber flare at day 4, complete resolution of pain at day 4, and mean change in anterior chamber cells at day 4). Each case maintained through day 15 with no need for rescue medication.

Dr. Edward Holland, professor of ophthalmology, University of Cincinnati and director, Cornea Service, Cincinnati Eye Institute, commented, "Rapid and effective relief of pain and inflammation is the key goal of the management of patients following ocular surgery. With proven safety and efficacy with a twice-a-day dosing regimen, KPI-121 1% will add an important tool to our post-operative armamentarium as a safe, effective, and convenient alternative to currently marketed topical corticosteroids, which are all recommended for dosing four times a day."

KPI-121 is a novel nanoparticle formulation of loteprednol etabonate utilizing Kala's proprietary mucus-penetrating particle (MPP) technology to enhance penetration into target tissues of the eye. In pre-clinical rabbit studies, MPP has been shown to increase loteprednol etabonate delivery into ocular tissues four-fold by facilitating penetration through the tear film mucus. KPI-121 has been studied in over 1,300 patients for the indications of temporary relief of the signs and symptoms of dry eye disease and the post-operative treatment of inflammation and pain following ocular surgery. Kala is currently conducting two phase 3 trials in dry eye disease with expected completion in 2017.

Kala is a biopharmaceutical company focused on the development and commercialization of therapeutics, using our proprietary MPP technology, with an initial focus on the treatment of eye diseases. In addition to KPI-121, Kala is evaluating compounds in its topically applied MPP receptor tyrosine kinase inhibitor program. Beyond ophthalmology, Kala's proprietary MPP technology has potential applications in women's reproductive health, respiratory and gastrointestinal diseases, and other indications.

Kala was founded by leaders in the fields of nanomedicine and biopharmaceutical engineering, and is backed by leading life sciences investors including OrbiMed, Longitude, Polaris, RA Capital Management, Vivo Capital, Third Rock Ventures, CAM Capital, Lux Capital, CVF, LLC, and Ysios Capital.

April

Tarveda to Present on Lead Intracellular Targeting Pentarin PEN-866 at 2017 American Association of Pharmaceutical Scientists National Biotechnology Conference

Business Wire: April 28, 2017 – WATERTOWN, MA, U.S.A. – Tarveda Therapeutics, Inc., a clinical stage biopharmaceutical company discovering and developing Pentarins™ as a new class of potent and selective cancer medicines, today announced that Dr. Mark Bilodeau, PhD, senior vice president of chemistry, will present data on PEN-866, the company's second Pentarin™ drug candidate, which targets the intracellular protein HSP90, at the 2017 American Association of Pharmaceutical Scientists (AAPS) national biotechnology conference, occurring May 1–3 at the San Diego Marriott Marquis and Marina in San Diego, CA. The presentation, titled "Exploiting the Preferential Accumulation of HSP90-Targeting Ligands in Tumors to Selectively Deliver Anti-Cancer Payloads," will take place from 10:40 am – 11:10 am PST on Monday, May 1, 2017, in the 'Hot Topic' session Inaugurating a New Era in Cancer Treatment—Intracellular Delivery.

"Dr. Bilodeau's presentation at AAPS continues to showcase our growing expertise in identifying and developing our Pentarins, potent and selective miniaturized drug conjugates that safely and effectively target anti-cancer payloads to solid tumors," said Drew Fromkin, president and chief executive officer of Tarveda. "The presentation will highlight our lead intracellular targeting conjugate, PEN-866, that binds to the intracellular target HSP90. In a broad range of tumor xenograft and patient-derived tumor models, PEN-866 demonstrated accumulation and retention of its potent payload SN-38 leading to cancer cell death and efficacy, which was clearly superior to that which was seen with irinotecan. We are excited about the prospects of PEN-866 and the potential to leverage our HSP90 franchise to enhance the performance of a number of high value payloads that have struggled to achieve efficacy in patients as single agents."

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PEN-866, which is designed to treat patients with solid tumor cancers including colorectal cancer, small cell lung cancer, and sarcoma, is scheduled to enter the clinic in 2017 via a phase 1/2a trial initially focused in patients with topo-1 inhibitor sensitive solid tumors. More information on PEN-866 can be found at www.tarveda.com.

Tarveda is developing Pentarins, potent and selective miniaturized drug conjugates with high affinity for specific cell surface and intracellular targets. Pentarins are engineered to bind to their tumor cell targets and provide sustained release of their potent therapeutic payloads deep into solid tumor tissue. Composed of a targeting ligand conjugated to a potent cell-killing agent through an optimized chemical linker, Pentarins are designed to overcome the deficits of both larger antibody drug conjugates and small molecules that limit their therapeutic effectiveness against solid tumors. Together, the components of Tarveda's Pentarins have distinct, yet synergistic, anticancer attributes: the small size of Pentarins allows for effective penetration and distribution into the tumor tissue, the ligand's targeting ability allows for specific binding and retention in tumor cells, and the chemical linker is tuned to optimize the release of the potent, cell-killing payload inside the cancer cells for efficacy.

Tarveda Therapeutics, Inc. discovers and develops Pentarins™, a new class of potent and selective miniaturized drug conjugates with enhanced targeting capabilities for the treatment of solid cancer tumors. Tarveda's lead Pentarin drug candidate, PEN-221, is a miniaturized drug conjugate that targets the somatostatin receptor 2 (SSTR2) for treatment of patients with neuroendocrine and small cell lung cancers. PEN-221 comprises a highly selective peptide that targets SSTR2 linked to the potent cytotoxic DM1 through a cleavable linker. Tarveda is also advancing its miniaturized HSP90 drug conjugate platform with lead candidate PEN-866, which comprises a small molecule HSP90 targeting ligand conjugated to SN-38, the highly potent, active metabolite of irinotecan. Tarveda's strategy includes developing its own proprietary Pentarins as well as applying the Pentarin platform to enhance the effectiveness of the targeting moieties and novel payloads of its pharmaceutical collaborators. www.tarveda.com

Braeburn Pharmaceuticals Achieves Primary Endpoint in Pivotal Phase 2/3 Study of BB0817, Risperidone 6-month Implant for Treatment of Schizophrenia

PRNewswire: April 26, 2017 – PRINCETON, NJ, U.S.A. – Braeburn Pharmaceuticals announced today that a 6-month study of the safety, tolerability, and pharmacokinetics of transferring patients diagnosed with schizophrenia or schizoaffective disorder and stabilized on oral risperidone to BB0817 (risperidone) implant has met its primary endpoint.

The trial was designed to demonstrate comparable average plasma concentrations of risperidone and its active metabolite, 9-hydroxy-risperidone between the risperidone implant and oral risperidone. The study enrolled more than 50 patients, diagnosed with schizophrenia or schizoaffective disorder according to DSM-V and stable on a daily 4 mg oral dose of risperidone for at least eight weeks. Enrolled patients received three risperidone implants just under the skin in their upper arm. The study met its objectives and demonstrated that plasma concentrations of oral risperidone and 9-hydroxy-risperidone were comparable to the plasma levels of BB0817 and remained consistent throughout the 6-month study.

"Schizophrenia is a potentially devastating disease, but it can be well-managed through compliance with antipsychotic medication. BB0817 may provide a compelling option to help patients manage schizophrenia, consistent with Braeburn's commitment to develop long-acting implantable and injectable treatments for stigmatized diseases where adherence is critically important," said Behshad Sheldon, president and CEO of Braeburn Pharmaceuticals. "This clinical program in schizophrenia represents a strong complement to our initial therapeutic focus in addiction and pain. Looking ahead, we expect results from a phase 3 risperidone safety study later this year and are targeting a year-end 2017 filing of a new drug application seeking approval for the risperidone implant."

Efficacy and safety of the risperidone implant were also assessed. During the trial, 100 percent of patients remained stable with no clinically meaningful change in positive and negative symptom scale (PANSS) scores from baseline over the course of the six months. The systemic adverse events were similar to those of oral risperidone and included akathisia (9%), EPS (6%), and anxiety (6%). Implant site pain was the most common adverse event related to the procedure (11%), and was generally mild in intensity. Nearly all (94%) patients who had the opportunity to enroll in an extension phase of the study chose to receive a second set of implants.

Risperidone is currently the leading agent used for treatment of schizophrenia; however, the utility of risperidone and other schizophrenia agents is dependent on consistent administration of therapeutic doses. Daily dosing of risperidone is particularly challenging for patients with schizophrenia where improvement in symptoms often leads to discontinuation of medication. Long-acting formulations of schizophrenia treatments are prescribed for approximately 23 percent of these patients, and are viewed as essential to optimizing patient outcomes. Although injectable formulations of risperidone are available, no FDA-approved formulation is currently available as a 6-month treatment.

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"Compliance with medication is a very important clinical issue, and without it, serious consequences including relapse and hospitalization are more likely. Preventing non-compliance is an important goal for any successful clinical treatment. The 6-month risperidone implant, if approved, would offer physicians and patients an innovative approach to the treatment of schizophrenia," said Rishi Kakar, M.D., associate medical director for Segal Institute for Clinical Research in Florida and principal investigator for the trial. "The implant is administered through a short, in-office procedure, and provides a treatment duration that is more than twice as long as currently-marketed injectables."

Schizophrenia is a serious disease characterized by a distortion in the process of thinking and of emotional responsiveness. It most commonly manifests as hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and is accompanied by significant social or occupational dysfunction. Onset of symptoms typically occurs in young adulthood and the condition is chronic, often requiring life-long treatment to mitigate symptoms.

It has been estimated that schizophrenia affects approximately 1 percent of the adult population in the U.S., and approximately 24 million people worldwide. In the U.S., schizophrenia is prevalent equally in both genders and accounts for approximately 20 percent of hospital bed stays. While there is no cure for the disease, symptoms and risk of relapse—the re-emergence or worsening of psychotic symptoms—can be managed in most patients with appropriate antipsychotic treatment. However, it is estimated that only 50 percent of patients who begin treatment with an antipsychotic remain on that treatment six months later, which can undermine long-term treatment outcomes.

Risperidone is an atypical (or second-generation) antipsychotic. It was first approved for treatment of schizophrenia by the FDA in 1994, and is marketed under the trade name Risperdal®. Risperidone is currently marketed in oral and injectable formulations, but there is no currently available implantable risperidone product and no formulation that delivers a stable dose for six months. The World Health Organization includes risperidone on its list of essential medicines, a list of the most important medications needed in a basic health system.

The implant platform technology enables subcutaneous insertion of a cylindrical, non-biodegradable, flexible polymer that can be used to deliver long-acting formulations of daily, oral drugs. This innovative technology, which was acquired by Braeburn in 2015, is designed to provide patients with a continuous and consistent level of medication over the course of a 6-month to one-year treatment regimen. The polymer membrane controls the rate of diffusion of the drug substance, thereby providing immediate release while improving drug delivery via controlled release. This technology is currently being used in development of the 6-month risperidone implant and a tizanidine implant.

Braeburn Pharmaceuticals, an Apple Tree Partners company, is a commercial-stage pharmaceutical company delivering individualized medicine in neuroscience. Long-acting therapeutic treatment options can be essential to improving patient outcomes and facilitating recovery in neurological and psychiatric disorders, which are often complicated by stigma and present significant public health challenges. Braeburn's commercial product, Probuphine® (buprenorphine) implant, was approved by the FDA in May 2016. Braeburn's investigational product pipeline consists of long-acting implantable and injectable therapies for serious neurological and psychiatric disorders, including opioid addiction, pain, and schizophrenia. Braeburn's pipeline products are at various stages of clinical development and include weekly and monthly CAM2038, subcutaneous injection depot formulations of buprenorphine, being investigated in opioid addiction and pain, BB0417 buprenorphine/granisetron injectable for acute pain, and BB0817, 6-month risperidone implant being investigated in schizophrenia. More information on Braeburn can be found at www.braeburnpharmaceuticals.com.

Mati Therapeutics Hits Major Milestone with 100 Patents

Business Wire: April 25, 2017 – AUSTIN, TX, U.S.A. – Mati Therapeutics, Inc. ("Mati") announced that its international patent portfolio now comprises 100 issued patents. Included in the portfolio is recently granted U.S. Patent No. 9,610,271 titled, "Sustained release delivery of active agents to treat glaucoma and ocular hypertension." The patent, which expires in 2033, contains subject matter related to a method for decreasing ocular pressure by implanting a lacrimal implant into one or both puncta (tear ducts) of the eye.

This newly issued patent further enhances Mati's patent portfolio, which consists of 100 issued patents and numerous patent applications to which Mati has exclusive rights in the U.S. and other major international markets. The patents cover 17 patent families, including important elements of Mati's Evolute® punctal plug delivery system for treatment of ocular indications. The Evolute® platform includes features for retaining the punctal plug within the nasolacrimal system of the eye during drug elution and sustained release formulations currently in development for the treatment of post-operative pain and inflammation. The proprietary technology has the potential to be used for multiple disease states with consistent, sustained efficacy.

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"The granting of 100 patents is a significant milestone for any company, but a very meaningful milestone for a small private company such as Mati. Our unique platform technology is under development for a number of indications including post-operative inflammation and pain, glaucoma and ocular hypertension, ocular allergy, and dry eye," said Bob Butchofsky, CEO of Mati. "Since its inception over four years ago, Mati has focused on innovation, and continues to build a significant intellectual property portfolio for sustained drug delivery platform covering the U.S., Europe, Canada, Japan, and China. We believe our patent portfolio provides Mati with a competitive advantage in research and development that will remain in place for many years to come."

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

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

Teva Launches AirDuo™ RespiClick® and Its Authorized Generic, Two Inhalers Containing Fluticasone Propionate and Salmeterol

Business Wire: April 20, 2017 – JERUSALEM, Israel – Teva Pharmaceutical Industries Ltd., (NYSE and TASE: TEVA) today announced the simultaneous launch of AirDuo™ RespiClick® (fluticasone propionate and salmeterol) inhalation powder and its authorized generic for the treatment of asthma in patients aged 12 years and older who are uncontrolled on an inhaled corticosteroid (ICS) or whose disease severity clearly warrants the use of an ICS/long-acting beta2-adrenergic agonist (LABA) combination.

AirDuo™ RespiClick® and its authorized generic are fixed-dose combination asthma therapies containing an ICS and a LABA, the same active ingredients as Advair®. The authorized generic is known as fluticasone propionate and salmeterol inhalation powder (multidose dry powder inhaler). Teva is launching both products at the same time in an effort to address the need for more affordable asthma treatment options in the U.S. Teva expects that sales of the authorized generic will represent most of the sales of the two products.

"With the launch of AirDuo™ RespiClick® and its authorized generic, our intent is to meet the needs of patients, providers, and payers in the U.S. seeking greater access to lower-cost asthma inhaler technology, while also allowing Teva to compete in the highly competitive asthma combination controller market," said Rob Koremans, M.D., president and CEO of global specialty medicines at Teva. "This important launch marks not only the first available generic ICS/LABA product in the U.S., but also the continued expansion of our RespiClick® family of products, which now includes breath-activated inhaler options for both maintenance treatment and rescue medication."

AirDuo™ RespiClick® was approved by the U.S. Food and Drug Administration (FDA) in January 2017 in three doses: 55/14 mcg, 113/14 mcg, and 232/14 mcg administered as one inhalation twice daily. AirDuo™ RespiClick® contains medication delivered via Teva's RespiClick® breath-activated, multi-dose dry powder inhaler (MDPI), which is used with other approved medicines in Teva's respiratory product portfolio.

NLS Pharma Announces Completion of Phase 2 Study for NLS-1, Its Lead ADHD Compound; New Investors, New Patents

PRNewswire: April 18, 2017 – STANS, Switzerland – NLS Pharma (NLS), a Swiss-based biotech group founded to develop first-in-class treatments for attention deficit hyperactivity disorder (ADHD) and other neurological disorders, today announced the following major milestones:

- Completion of the phase 2 study NLS-1001, a double-blind placebo-controlled study to determine the efficacy, safety, tolerability and pharmacokinetics of a controlled release (CR) formulation of NLS-1 (mazindol) in adults with DSM-5 ADHD. NLS-1 is a potential alternative to stimulants for the treatment of ADHD. Phase 2 results will be available in the coming weeks.

continued

- NLS Pharma just completed a series B funding round of an undisclosed amount whose proceeds will support continued progression of NLS-1 towards phase 3 clinical trials.
- NLS recently secured four new patents within its ADHD franchise for the U.S., Europe, and Japan.

NLS welcomes the following group of new investors and advisors who participated in the series B funding round and bring a wealth of scientific authority, research & development, business development, and commercialization experience:

- Thomas Ebeling, CEO & president, ProSiebenSat.1 Media SE, and a 20-year biopharmaceutical industry veteran whose extensive worldwide leadership positions include serving as CEO of the global pharmaceutical business at Novartis.
- Professor Claus Christiansen, MD, co-founder and chairman of the Nordic Bioscience Group, as well as a distinguished scientist, successful entrepreneur, and founder of the Center for Clinical and Basic Research (CCBR).
- Hervé Girsault, formerly global head of mergers & acquisitions, business development and strategy at Novartis Consumer Health, among other global leadership positions at the company.

"NLS pairs an increasingly rare new investment opportunity in a potentially large market with an investigational compound that has already completed phase 2," said Thomas Ebeling. "The ADHD patient population is vast, underserved, and there is a need to reduce systemic reliance on traditional stimulants with alternative treatments that may enable long-term administration. I am impressed by the speed with which NLS Pharma has advanced NLS-1 to date, and look forward to contributing to its potential continued success."

"My investment strategy usually focuses on projects for Nordic Bioscience Group," said Dr. Claus Christiansen. "But after I was introduced to the people, unique approach, and fast-moving programs at NLS Pharma I couldn't pass up this opportunity to help potentially transform the treatment paradigm in ADHD, as this condition impairs the quality of life for a large population in the world and requires novel alternative solutions."

"These are exciting times at NLS Pharma and we are grateful for this demonstration of confidence from such a dynamic and experienced group of new investors who will enrich the expertise and resources required to execute our aggressive strategy," said Alex Zwyer, CEO at NLS Pharma Group. "The clinical progress to date of NLS-1 is one source of great optimism, and the outlook for our ADHD franchise as a whole is further brightened by new patents and our broader pipeline."

NLS Pharma (NLS) is a privately owned, Swiss-based biotech group focusing on compounds to treat ADHD, sleep disorders, and cognitive impairment. Our aim is to create new approaches to treat mental and behavioral disorders and enhance cognitive function in healthy people. NLS Pharma is a privately owned enterprise managed by a top level team of experts who have demonstrated their value and experience with large pharmaceutical companies, and work closely with ADHD and sleep-related disorders key opinion leaders.

Aurinia Completes Licensing Deal with Merck Animal Health for Its Nanomicellar Formulation of Voclosporin for the Treatment of Canine Dry Eye Syndrome

Business Wire: April 17, 2017 – VICTORIA, BC, Canada – Aurinia Pharmaceuticals Inc. (NASDAQ: AUPH/TSX: AUP) ("Aurinia" or the "company") today announced that it has signed a definitive agreement ("the agreement") granting Merck Animal Health, known as MSD Animal Health outside of the United States and Canada, worldwide rights to develop and commercialize Aurinia's patented nanomicellar voclosporin ophthalmic solution (VOS) for the treatment of dry eye syndrome in dogs.

Under the terms of this agreement, Aurinia will receive an upfront payment and is eligible to receive further payments based on certain development and sales milestones. Furthermore, Aurinia will receive royalties based on global product sales. Merck Animal Health will be responsible for the remaining clinical development and commercialization of VOS for use in the animal health field, while Aurinia retains all human health rights. The companies will share in the final work product and any technical knowledge that may be generated during the collaboration.

"This partnership with Merck Animal Health underscores our long-standing belief that voclosporin has the potential to be effectively used across a range of therapeutic areas, in addition to its primary potential indication for the treatment of lupus nephritis," said Richard Glickman, Aurinia's CEO and chairman of the board. "In addition to enhancing dry eye treatment options in the animal health field, VOS has a differentiated product profile with long patent life that has the potential to compete in the multi-billion dollar human prescription dry eye market. While this ophthalmology project will continue to be advanced by Merck Animal Health, the Aurinia clinical team will remain focused on our lupus nephritis program, which is on track to begin enrollment for the AURORA phase III trial this quarter."

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Throughout the past year, Merck Animal Health has conducted proof of concept research in dogs suffering from dry eye syndrome, which affects one out of every 22 dogs. The early symptoms can be easily missed by pet owners, leading to irreversible damage to a dog's vision and eventually resulting in blindness.

"VOS has the potential to address significant unmet medical needs in ophthalmology, and the preliminary results of our canine dry eye trial are very promising," says Holger Lehmann, DVM, PhD, associate vice president, drug discovery, Merck Animal Health. "We look forward to continuing our collaboration with Aurinia and believe this partnership is a prime example of the synergies that exist between human and animal health drug development for the benefit of all of our patients."

"Completed preclinical and human phase Ib studies using Aurinia's nanomicellar VOS formulation have shown encouraging results in terms of delivery of active drug to the target tissues of the eye," said Neil Solomons, MD, chief medical officer of Aurinia. "The nanomicellar formulation enables high concentrations of voclosporin to be incorporated into a preservative-free solution for local delivery to the ocular surface. This has been shown to potentially improve efficacy, dosing frequency, and tolerability versus the current treatments for dry eye syndrome. We are excited about the potential for topical ocular administration of voclosporin utilizing this unique and proprietary nanomicellar drug delivery technology."

Aurinia is exploring all options to create value with its proprietary nanomicellar ocular formulation of voclosporin in the human health field including, but not limited to, further development, out-licensing, or divestiture while remaining focused on the phase III lupus nephritis program.

Keratoconjunctivitis sicca (KCS or dry eye) is a common eye disease of dogs. This disease is characterized by inflammation of the lacrimal glands, resulting in reduced or absent tear formation and secondary bacterial conjunctivitis. If left untreated, damage to the tear glands is irreversible, leading to painful dry eye, and often leads to permanent blindness.

Dry eye syndrome (DES), also known as keratoconjunctivitis sicca (KCS), is a multifactorial, heterogeneous condition wherein the eyes have insufficient amount of tears, which are necessary for normal eye function. Prevalence estimates range from 14% to 33% of the general population, with between 30 and 40 million people believed to be affected in the U.S. It is one of the most common reasons for visits to ophthalmologists. DES prevalence is likely to continue to grow as a result of the ageing population (risk of DES increases 35% each decade after age 40), higher physician and patient awareness, increasing visual tasking, and worsening environmental conditions.

Aurinia is a clinical stage biopharmaceutical company focused on developing and commercializing therapies to treat targeted patient populations that are suffering from serious diseases with a high unmet medical need. The company is currently developing voclosporin, an investigational drug, for the treatment of lupus nephritis (LN). The company is headquartered in Victoria, BC, and focuses its development efforts globally. www.auriniapharma.com

For over a century, Merck has been a global health care leader working to help the world be well. Merck Animal Health, known as MSD Animal Health outside the United States and Canada, is the global animal health business unit of Merck. Through its commitment to the Science of Healthier Animals™, Merck Animal Health offers veterinarians, farmers, pet owners, and governments one of the widest range of veterinary pharmaceuticals, vaccines, and health management solutions and services. Merck Animal Health is dedicated to preserving and improving the health, well-being, and performance of animals. It invests extensively in dynamic and comprehensive R&D resources and a modern, global supply chain. Merck Animal Health is present in more than 50 countries, while its products are available in some 150 markets. For more information, visit www.merck-animal-health.com or connect with us on LinkedIn, Facebook, and Twitter at @MerckAH.

Ironshore Pharmaceuticals Announces Positive HLD100 Results from Open-Label Tolerability Study in Pediatric ADHD Patients

Business Wire: April 12, 2017 – GEORGE TOWN, Grand Cayman – Ironshore Pharmaceuticals & Development, Inc. ("Ironshore"), a wholly owned subsidiary of Highland Therapeutics Inc., today announced that it has presented to the U.S. Food and Drug Administration ("FDA") the results from an open-label clinical trial that was conducted to investigate the tolerability and efficacy of HLD100 – a novel delayed-release, extended-release ("DR/ER") formulation of amphetamine currently under development as a potential new treatment option for patients with attention-deficit/hyperactivity disorder ("ADHD").

HLD100 was well tolerated with no serious adverse events noted during the study. The majority of side effects were mild or moderate in severity and resolved during the course of the treatment. Given the novelty of HLD100's evening administration, and to probe for any potential impact on sleep, the sleep disturbance scale for children ("SDSC") was used. Importantly, the results showed median values for the SDSC total score and all subscale scores either the same or lower (improved) than at baseline.

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"The dedicated employees at Ironshore have worked tirelessly over the past several years to develop a novel medication that may provide improved clinical outcomes for ADHD patients and their caregivers," said David Lickrish, Ironshore's chief executive officer. "With the FDA's PDUFA action date for our other investigational ADHD drug, HLD200 (methylphenidate DR/ER), coming later this year, Ironshore is reaffirming its commitment to families and developing an additional treatment option. Similar to HLD200, which was evaluated in 10 clinical studies, including two pivotal trials, our amphetamine program is equally ambitious and will evaluate HLD100 in two large pivotal trials, which may help to inform the public regarding its unique value proposition and its potential to become a first-line treatment option in ADHD, if approved."

The HLD100-103 clinical trial enrolled 22 pediatric patients (ages 6 to 12) in a single center in the U.S. Patients were titrated over a five-week period to evaluate (i) optimal dosage strength and (ii) optimal clinical effects. Similar to the HLD200 (methylphenidate DR/ER) pivotal studies, Ironshore used the before school functioning questionnaire ("BSFQ") and the parent rating of evening and morning behavior – revised ("PREMB-R") morning ("AM") and evening ("PM") subscales, as well as the ADHD-RS-IV scale as assessment tools. The Weiss functional impairment rating scale ("WFIRS") was also used.

The average dosage strength in the study was 25.9 mg, which is below the recommended maximum dose for other amphetamine formulations. Importantly, a clinical effect was observed upon awakening that lasted through to the evening bedtime routine period. Our pivotal studies will further evaluate the observed preliminary signals that HLD100 may have a long duration of action without any discernible rebound effects that are sometimes reported with stimulant medications.

At baseline, ADHD-RS-IV, BSFQ, PREMB-R AM, and PREMB-R PM scores were 36.1, 28.6, 5.8, and 14.1, respectively. Following five weeks of treatment, these scores improved to 13.3, 8.8, 1.5, and 5.7, respectively; representing an improvement of 63%, 68%, 74%, and 60%, respectively. On the WFIRS scale, scores improved from 48.5 at baseline to 27.7 at the end of the study, representing a 43% improvement in functioning.

The results of the HLD100-103 study were reviewed at an end of phase 2 meeting with the FDA. Based on feedback we received at the meeting with FDA, Ironshore is pursuing a clinical program for HLD100 that will include two pivotal phase 3 studies. Results from these studies, if successful, may demonstrate replication of effect during specific time periods, which could result in a differentiated drug label. Ironshore intends to initiate the pivotal trials in the third quarter of 2017, with a new drug application expected in 2018.

Dr. Randy Sallee, Ironshore's chief medical officer and author of more than 100 journal articles on ADHD, said, "The results from the HLD100-103 study are better than anticipated and further validate Ironshore's investment in pursuing a new approach to the treatment of ADHD. As a science-driven organization, we are pleased to continue to build on the development path of HLD200, which I believe is the first product in clinical trials to demonstrate significant improvements in each of early morning, late afternoon, and evening impaired functioning with a single dose of a long-acting stimulant in children with ADHD."

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

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

Frequency Therapeutics Announces $32 Million Series A Financing to Support Clinical Development of a First-in-Class Hearing Restoration Therapeutic

Business Wire: April 11, 2017 – WOBURN, MA, U.S.A. – Frequency Therapeutics, a company developing a pipeline of new drugs that activate progenitor cells within the body, today announced the closing of a $32 million series A financing. The funding round was led by CoBro Ventures. Additional participating investors included Morningside Ventures, Emigrant Capital Corp., Korean Investment Partnership, Alexandria Real Estate Equities, and other U.S. and international investors.

Frequency was founded in 2015 to advance the breakthrough work in progenitor cell activation (PCA™) by Robert Langer, Sc.D., and Jeffrey Karp, Ph.D., at the Massachusetts Institute of Technology (MIT) and Harvard Medical School. Using its proprietary PCA platform, Frequency's lead product candidate stimulates the regrowth of sensory hair cells in the inner ear to treat chronic noise induced hearing loss. The foundational science by Frequency's co-founders has been widely published, including a publication in Nature Methods (2014) and most recently as a cover feature in February's Cell Reports (2017). Frequency has a worldwide exclusive

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license to related intellectual property from MIT and Partners Healthcare, and intends to pursue the potential application of PCA for a wide range of therapeutic indications including hearing loss, skin disorders, muscle regeneration, and gastrointestinal diseases.

"Bob Langer and Jeff Karp's vision is to gain much of the same effect as gene therapy and CRISPR by using small molecules, which we believe are safer and allow for easier delivery. Our data is very compelling and we are excited to be moving to the clinic in the next 12 to 18 months," said Marc Cohen, co-founder of CoBro Ventures and chairman of Frequency's board of directors, which was announced in January 2017. "Hearing loss is not just a symptom of aging, but an indication that affects a significant percentage of the world's population in people of all ages. The U.S. loses on average $56 billion in annual productivity due to the complications associated with chronic noise-induced hearing loss alone."

"With no effective therapy available, this presents an enormous market opportunity and we believe there is even broader potential in indications beyond hearing loss with the further development of the PCA platform. Frequency is building a next-generation regenerative medicine company with a truly breakthrough approach designed to awaken the body's innate ability to restore function to damaged or diseased tissues," said David Lucchino, co-founder, president, and CEO of Frequency.

Most hearing deficits result from the loss of key cells in the inner ear, called sensory hair cells, which are necessary to convert sound waves into nerve impulses. In adult mammals, unlike birds or reptiles, these cells do not spontaneously regenerate, although progenitor cells capable of regenerating hair cells remain present in the ear. Chronic noise induced hearing loss, Frequency's lead program, is a significant unmet need with no therapeutic approved for the condition. Around 48 million people are affected in the U.S. alone and the World Health Organization (WHO) estimates that 1.1 billion people are at risk for hearing loss from recreational noise alone. Hearing loss caused by prolonged exposure to excessive noise can be attributed to many professional environments, such as heavy construction sites or military training, but every day loud noises such as a busy subway, weekend concerts, and even the use of headphones can have a large impact on hearing. Frequency's therapeutic candidate for noise induced hearing loss is a proprietary combination of small-molecule drugs to transiently activate inner ear progenitor cells so that they multiply and create new hair cells.

Frequency's precise and controlled approach transiently causes Lgr5+ progenitor cells to divide and differentiate, much like what is seen in naturally regenerating tissues such as the skin and intestine. Frequency activates 'stemness' through mimicking signals provided by neighboring cells (the stem cell niche) with small molecules, and this proprietary approach is known as the progenitor cell activation (PCA™) platform. Frequency believes that PCA has the potential to yield a whole new category of disease-modifying therapeutics for a wide range of degenerative conditions. To fuel its drug discovery programs, Frequency is leveraging a PCA screening platform using primary human cells, including cochlear progenitor cells and adult human progenitor cells from the GI tract. Frequency's initial focus is on chronic noise induced hearing loss. Other potential applications include skin disorders, muscle regeneration, and gastrointestinal diseases.

Frequency Therapeutics develops small molecule drugs that activate progenitor cells within the body to restore healthy tissue. Through the transitory activation of these progenitor cells, Frequency enables disease modification without the complexity of genetic engineering. Our lead program re-creates sensory cells in the inner ear to treat chronic noise induced hearing loss, which affects over 30 million people in the U.S. alone. www.frequencytx.com.

Ferring Announces Exclusive Agreement with Alrise Biosystems for the Development of an Injectable, Controlled-Release Peptide

Business Wire: April 10, 2017 – SAINT-PREX, Switzerland – Ferring Pharmaceuticals and Alrise Biosystems announced today that the companies have entered into a development agreement with exclusive option rights for Ferring to leverage Alrise's ImSus® Technology Platform for the development of an injectable, controlled-release formulation of a peptide therapeutic.

Under the terms of the agreement, Alrise will conduct feasibility and scale-up studies with Ferring. Upon completion of the development work, Ferring will have the right to exercise its option and enter into a definitive agreement with Alrise to further develop and manufacture the formulation.

"Ferring aims to harness innovative technology platforms, such as Alrise's microparticle-technology platform, in order to provide new, controlled-release formulations of peptides and proteins for our patients," said Alan S. Harris, senior vice president, R&D executive office, Ferring Pharmaceuticals. "Controlled, long-duration release treatments can maximise efficiency, help improve compliance to treatment, and make life simpler for our patients."

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"Alrise is committed to delivering solutions that enhance the performance of drug products in development," said Volker Rindler, head of business development and co-founder, Alrise Biosystems. "Together with Ferring we aim to develop a new depot formulation that, once injected, releases the drug in a controlled way and thereby ensures an effective drug level over several months."

Ferring recently announced a number of agreements aimed at developing new formulations of peptide-based therapeutics through novel technology platforms, including a long-term collaboration with Aché Laboratórios Farmacêuticos, aimed at improving the bioavailability, efficacy, and safety profile of oral therapeutic medicines through nanotechnology.

ImSus® is a unique drug delivery technology platform for the design and manufacture of drug-loaded polymeric nano- and microparticle formulations. The patented process allows an efficient encapsulation of small molecule, peptide, and protein drugs for injectable controlled release applications. Key advantages of the ImSus® technology include the exclusive use of non-harmful (non-carcinogenic) organic solvents and the control over critical performance attributes, which aim to shorten product development times and lower costs.

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

Alrise was founded in 2004 by Dr. Celal Albayrak, Dr. Volker Rindler, and Dr. Heiko Seemann. In collaboration with pharmaceutical companies, Alrise develops injectable as well as oral formulations based on polymeric nano- and microparticles for various substance classes. Major shareholders in the Berlin-based company are the VC companies Creathor Venture and IBB Beteiligungsgesellschaft mbH as well as Dr. Giuseppe Vita, the former CEO of Schering AG. For more information, visit www.alrise.de.

Therapix Signs Exclusive License Agreement with Yissum for Nasal Drug Delivery Technology

PRNewswire: April 5, 2017 – TEL-AVIV, Israel – Therapix Biosciences Ltd. (NASDAQ, TASE: TRPX), a specialty clinical-stage pharmaceutical company specializing in the development of cannabinoid-based drugs, today announced that it has signed a sublicense agreement for Yissum Research Development Company of the Hebrew University Ltd.'s nasal drug delivery technology.

Under the terms of the agreement, Yissum will grant Therapix an exclusive, worldwide, sub-licensable, royalty-bearing license to its technology for the nasal delivery of cannabinoids.

The technology, developed by Professor Elka Touitou from the Institute of Drug Research at the Hebrew University of Jerusalem, facilitates administration and effective nasal absorption of tetrahydrocannabinol, or THC, the active pharmaceutical ingredient in the drugs developed by Therapix.

"This agreement with Yissum paves the way for the development and marketing of new cannabinoid-based treatment offerings for people suffering from a variety of neurological conditions," said Therapix CEO Dr. Elran Haber. "Compared with standard oral administration, we expect the nasal delivery technology developed by Professor Touitou and her team at Hebrew University to offer improved bioavailability, efficacy, and a shorter reaction time for patients."

The license agreement with Yissum has the potential to advance Therapix's strategy to develop proprietary cannabinoid delivery technologies to improve drug administration, including nasal and sublingual delivery methods for THC, with formulations designed to increase efficacy.

Therapix Biosciences Ltd. is a specialty clinical-stage pharmaceutical company led by an experienced team of senior executives and scientists, focused on creating and enhancing a portfolio of technologies and assets based on cannabinoid pharmaceuticals. With this focus, the company is currently engaged in two internal drug development programs based on repurposing an FDA-approved synthetic cannabinoid (dronabinol): Joint Pharma, developing THX-TS01 targeted to the treatment of Tourette's syndrome; and BrainBright Pharma, developing THX-ULD01 targeted to the high value and under-served market of mild cognitive impairments. More information is available online at http://www.therapixbio.com.

Gurnet Point L.P. Enters into Agreement to Acquire Innocoll Holdings plc

Business Wire: April 4, 2017 – CAMBRIDGE, MA, U.S.A., and ATHLONE, Ireland – Gurnet Point L.P., a healthcare investment fund, and Innocoll Holdings plc (NASDAQ: INNL), a global pharmaceutical and medical device company, today announced that they

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have reached an agreement on the terms of a recommended offer. Under the recommended offer, Gurnet Point will acquire Innocoll for $1.75 per share in cash, and up to $4.90 in cash from a contingent value right (CVR), for a total potential per share value of up to $6.65 or up to approximately $209 million in aggregate. The initial cash consideration of $1.75 represents a premium of approximately 120 percent to the closing price per Innocoll Share on March 10, 2017, the last dealing day prior to the date on which the anomalous movement in Innocoll's shares commenced (and a premium of approximately 28 percent to the closing price per Innocoll Share on March 15, 2017, the day prior to Innocoll initiating the commencement of the offer period).

During the offer period, Gurnet Point plans to provide a term loan of $10 million to give Innocoll additional resources needed for the continued development of XARACOLL within the post-operative pain market. Innocoll believes that the loan will provide it with the additional capital needed to prepare for the re-submission of the XARACOLL new drug application ("NDA") to the U.S. Food and Drug Administration ("FDA") in order to achieve the milestones related to the CVR.

This transaction builds on Gurnet Point's strategy of investing in life science, medical technology, and healthcare service companies. Since its initial NASDAQ public offering in 2014, Innocoll has leveraged its proprietary collagen-based technology to successfully complete two phase 3 studies for XARACOLL, Innocoll's late-stage surgically implantable and bioresorbable collagen matrix. XARACOLL was developed to provide sustained post-operative pain relief through controlled delivery of bupivacaine at the surgical site.

Innocoll noted that its board had explored a sale of the company, to achieve its goal of bringing XARACOLL to market, as well as keeping the company independent and funding the over $100 million required to fund operations through 2019 from raising equity or debt. The "go-it-alone" option was dismissed due to the potential for significant shareholder dilution and execution risk. A potential license for XARACOLL in the United States was also investigated, but no suitable partner has been found.

"Having studied a number of strategic options over the past several months, our board and management team believe this strategic transaction will give Innocoll access to the financial resources it needs to pursue its goals of bringing XARACOLL through its development to commercialization, and address important unmet medical needs in the post-operative pain market. We believe that the combined leadership of the two companies, supported by Gurnet Point's financial strength, will better position Innocoll to pursue a successful filing and subsequent commercialization of XARACOLL," said Jonathan Symonds, chairperson of Innocoll. "The Innocoll directors unanimously support the offer, which represents a significant premium to the recent share price. In addition, the CVR allows shareholders to participate in the continued development of XARACOLL without further investment."

The directors of Innocoll and major shareholders, including holdings managed by Fortress, Morgan Stanley, Sofinnova, and Unique Technologies, have provided irrevocable undertakings to vote in favor of the scheme. In total, management, directors, and shareholders have provided irrevocable undertakings representing 46% of the issued ordinary share capital of Innocoll. Details of these irrevocable undertakings, including the circumstances in which they cease to be binding, are set out in the announcement pursuant to Rule 2.5 of the Irish Takeover Rules made by Gurnet Point, Gurnet Bidco, and Innocoll today.

"Gurnet Point intends to work with Innocoll's team to help bring XARACOLL to market by infusing substantial additional capital for its continued development and regulatory approval. We have great respect for Tony Zook and his team at Innocoll and look forward to investing in the business and assisting with the approval of XARACOLL and its commercialization," said Christopher Viehbacher, managing partner at Gurnet Point Capital.

Innocoll had expected to receive FDA approval of XARACOLL this year. On December 29, 2016, Innocoll announced that it had received a refusal to file letter from the FDA for XARACOLL. Among other points, the FDA indicated that XARACOLL should be characterized as a drug-device combination product and that additional clinical and nonclinical information on XARACOLL may be required. To provide this information, Innocoll proposes to conduct an additional short-term pharmacokinetic study and several short-term non-clinical toxicology and biocompatibility studies.

The Innocoll directors believe that, if adequately financed and successful, such studies may be completed in time for an end of year re-submission of the XARACOLL NDA. Data from these studies, along with additional manufacturing information required to address the new combination product designation by the FDA and other chemistry, manufacturing, and control activities, are also expected to be included in the re-submission.

If the re-submitted NDA is accepted by the FDA, thereby allowing XARACOLL to ultimately be approved, the Innocoll directors believe that Innocoll could be in a position to commercialize XARACOLL by the end of 2018.

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ViaCyte and W. L. Gore & Associates Announce Collaborative Research Agreement to Develop Novel Implantable Delivery Technologies for Cell Therapies

PRNewswire: March 29, 2017 – SAN DIEGO, CA, and NEWARK, DE, U.S.A. – ViaCyte, Inc., a privately held regenerative medicine company, and W. L. Gore & Associates, Inc. ("Gore"), a global materials science company, today announced a collaborative research agreement whereby the two companies will work together to develop novel implantable cell therapy delivery device technologies that provide protection from immune rejection.

For more than a decade, ViaCyte has been developing innovative stem cell-derived cell replacement therapies with a focus on the treatment of insulin-requiring diabetes. In the case of patients with type 1 diabetes, ViaCyte's product candidates have the potential to provide a functional cure. The company was the first to describe directed differentiation of human pluripotent stem cells into pancreatic cells, and the first to demonstrate the differentiation of stem cell-derived pancreatic progenitor cells into glucose-responsive insulin-producing cells, both *in vivo* and *in vitro*. In addition, ViaCyte launched the first clinical trial for stem cell-derived islet replacement therapy for type 1 diabetes. An important aspect of the therapy is the effective delivery of the cells to the patient. To accomplish this, ViaCyte has been developing encapsulation technologies including devices that protect the cells from the host immune system.

For more than forty years, Gore has been applying its materials science expertise to a variety of specific challenges in the life science industry. "We have a proven track record of developing and commercializing innovative new materials and products to address challenging implantable medical device applications and solving difficult problems for biologics manufacturers. Gore and ViaCyte began exploring a collaboration in 2016 with early encouraging progress leading to this agreement, and it was clear to us that teaming up with ViaCyte provided a synergistic opportunity for both companies," said Edward Gunzel, technical leader for Gore PharmBIO Products. "The experience, expertise, and intellectual property that each of us bring to the table is highly complementary. We look forward to working with ViaCyte to develop novel implantable delivery technologies for cell therapies."

ViaCyte is developing the PEC-Encap™ (also known as VC-01™) product candidate designed to deliver stem cell-derived islet replacement therapies to patients with type 1 diabetes as well as patients with type 2 disease that require insulin. The PEC-Encap combination product comprises PEC-01 pancreatic progenitor cells delivered in an immune-protective device called the Encaptra® cell delivery system. Based upon early, preliminary clinical evaluation, the PEC-Encap product appears safe, the Encaptra device is providing immune protection as designed, and evidence of vascularization, engraftment, and differentiation of the PEC-01 cells into insulin-producing beta cells has been observed. Further product development work remains to improve engraftment of PEC-Encap, and non-clinical and clinical results have indicated the potential for improvement through modifications to the Encaptra device.

Building on the observations with the PEC-Encap product candidate, ViaCyte is initiating clinical development of the PEC-Direct product candidate. The PEC-Direct product also delivers PEC-01 cells, but in a device that allows for direct vascularization of the cells. Used with immunosuppression as with other transplants, PEC-Direct has the potential to be a functional cure for patients suffering with type 1 diabetes who are at high risk for life-threatening acute complications.

"Gore has expertise in medical device development and drug delivery technologies, as well as previous research and development experience on cell encapsulation and implant programs for diabetes. We believe this collaboration represents a mutually beneficial relationship as the two teams cooperatively establish new methods of effectively delivering cell therapy to those with major unmet medical needs," said Paul Laikind, PhD, president and CEO of ViaCyte. "As ViaCyte advances our next generation encapsulation technologies for cell therapies, Gore's contribution to the material and design improvements of the Encaptra delivery system is expected to support the reliable and robust long-term engraftment that is required for the PEC-Encap product to be most effective. With Gore's help, we plan to improve on the results we have seen with PEC-Encap, which would then have the potential of benefiting all patients with insulin-requiring diabetes, both type 1 and type 2."

ViaCyte and Gore have established a joint development team with members from both companies. Other terms of the agreement were not disclosed.

W. L. Gore & Associates is a global materials science company dedicated to transforming industries and improving lives. Founded in 1958, Gore has built a reputation for solving complex technical challenges in the most demanding environments—from revolutionizing the outerwear industry with GORE-TEX® fabric to creating medical devices that improve and save lives to enabling new levels of performance in the aerospace, pharmaceutical, and mobile electronics markets, among other industries. The company is also known for its strong, team-oriented culture and continued recognition from the Great Place to Work® Institute. Headquartered in

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Newark, Delaware, Gore employs approximately 10,000 associates and generates annual revenues that exceed $3 billion. For more information on Gore, please visit www.gore.com

ViaCyte is a privately held regenerative medicine company developing novel cell replacement therapies as potential long-term diabetes treatments to reduce the risk of hypoglycemia and diabetes-related complications. ViaCyte's product candidates are based on the derivation of pancreatic progenitor cells, which are then implanted in a durable and retrievable cell delivery device. Once implanted and matured, these cells are designed to secrete insulin and other pancreatic hormones in response to blood glucose levels. ViaCyte has two products in development. The PEC-Direct™ product candidate delivers the pancreatic progenitor cells in a non-immunoprotective device and is being developed for type 1 diabetes patients that have severe hypoglycemic episodes, extreme glycemic lability, and/or impaired awareness of hypoglycemia. The PEC-Encap™ (also known as VC-01) product candidate delivers pancreatic progenitor cells in an immunoprotective device and is currently being evaluated in a phase 1/2 trial in patients with type 1 diabetes who have minimal to no insulin-producing beta cell function. ViaCyte is headquartered in San Diego, California, with additional operations in Athens, Georgia. The company is funded in part by the California Institute for Regenerative Medicine (CIRM) and JDRF. For more information on ViaCyte, please visit www.viacyte.com.

Nuvo Pharmaceuticals™ Enters into Pennsaid® 2% License Agreement with Sayre Therapeutics PVT Ltd. for India, Sri Lanka, Bangladesh, and Nepal

PRNewswire: March 28, 2017 – MISSISSAUGA, ON, Canada – Nuvo Pharmaceuticals Inc. (Nuvo or the company) (TSX: NRI), a commercial healthcare company with a portfolio of commercial products and pharmaceutical manufacturing capabilities, today announced that it has entered into an exclusive license agreement with Sayre Therapeutics PVT Ltd. (Sayre Therapeutics) to distribute, market, and sell Pennsaid 2% in India, Sri Lanka, Bangladesh, and Nepal (the territory). Nuvo has received an upfront payment and is eligible to receive milestone payments and a double-digit royalty on net sales. Nuvo will supply Pennsaid 2% to Sayre on an exclusive basis from its manufacturing facility in Varennes, Québec.

"We are extremely pleased that our very capable and committed new partner, Sayre Therapeutics, will represent the Pennsaid 2% brand in this significant South Asian region," said Jesse Ledger, Nuvo's president. "We expect to complete Pennsaid 2% out-licensing agreements for other territories throughout 2017 and 2018. Our strategy is to make Pennsaid 2% a global brand which will increase and diversify our revenue streams and increase capacity utilization at our manufacturing facility."

Shukrit Chimote, CEO, Sayre Therapeutics said, "Our collaboration with Nuvo helps us bring a U.S. FDA approved best-in-class solution to South Asia. Pennsaid adds an additional first-line treatment option to our growing portfolio of rheumatology medicines. Pennsaid 2% will greatly benefit the South Asian patient community and improve their quality of life."

The license agreement grants Sayre the exclusive right throughout the territory to market, sell, and distribute Pennsaid 2% as a prescription drug for the human treatment of osteoarthritis of the knee and acute pain from sprains and strains. Nuvo will provide Sayre with its existing Pennsaid 2% regulatory dossier and the U.S. Food and Drug Administration (FDA) approval of Pennsaid 2% which Sayre will use to support its application for regulatory approvals in the countries within the territory. ■