CRS Leading Delivery Science and Technology

Newsletter

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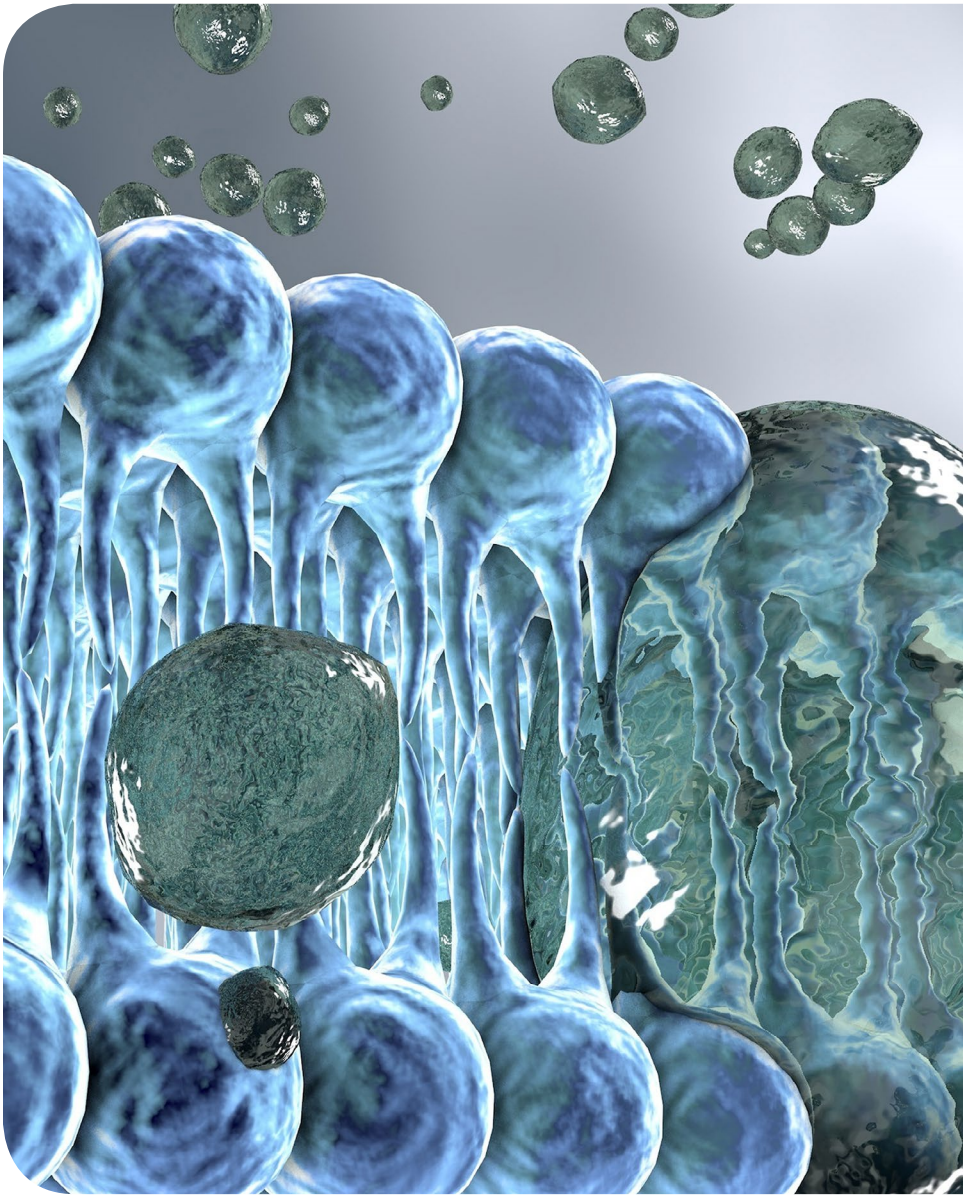
What's Inside

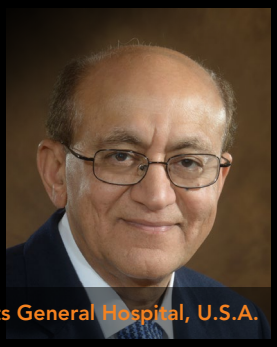


NYC

Controlled Release Society Annual Meeting & Exposition

July 22–24, 2018 | New York, NY, U.S.A.

2018 Plenary Speakers Announced



Rakesh **Jain**

Massachusetts General Hospital, U.S.A.

Kinam **Park**

Purdue University, U.S.A.

Molly **Stevens**

Imperial College London, UK

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CRS Newsletter

Leading Delivery Science and Technology

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

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Bozena Michniak-Kohn
Ernest Mario School of Pharmacy
Rutgers–The State University of New Jersey, U.S.A.

Are You *Attending* This Conference?

We are constantly inundated with offers for internet seminars, discussion groups, and short meetings on interesting topics. These are pitched as convenient since you can access them often at any time, even post event, on any device with no flight delays, hotel costs, or loss of several days for travel out of the office. Sounds good all around. So why do we still make an effort to pack our bags and all our computing equipment together with piles of work, arrange for caregivers at home, and travel cross country to that conference? I decided for our discussion today to look into this in more detail.

First, in spite of the internet "conveniences" we are social animals (even though the public thinks that scientists and particularly academically oriented members of this species are lone wolves). My more in-depth look into reasons for conference attendance yielded I believe the answers to their value to us as scientists in spite of the financial constraints we all face with travel funds.

One of the many reasons for attending conferences is that scientists can share their data and get in-person feedback from other participants on improving their work, a reason many young scientists identify as one of their top motivations. Then there are the learning from other researchers' papers and oral presentations and the chance to learn about new topics, methods, applications, and interpretations as well as new related areas. Often new collaborators are located at conferences, and sometimes we may arrange new studies with groups from areas of science that we had not considered before. Finally, there is the networking that many of us value so much and the opportunity of meeting new people, some of them known only by names from their published papers in journals.

Some additional thoughts from young investigators are taken from an article by Elizabeth Pain titled "How to Get the Most out of Attending Conferences" (www.sciencemag.org/careers/2017/05/how-get-most-out-attending-conferences):

"I find conferences rejuvenating. They are inspirational and energizing opportunities to connect with the greater scientific community, think about new strategies to approach my research, contemplate the bigger picture, and establish collaborations. A good conference has the capacity to bring a scientist, no matter their career stage, out of a slump."

Tenaya Vallery, doctoral candidate at Yale University

"Papers usually make it seem like the experimental results discovered themselves, and going to conferences allows me to find out about the human motivation and broader context. I also like getting new perspectives on science, making new friends (as life as a graduate student can be a little insular), and the chance to discover a new city."

Julian West, doctoral candidate at Princeton University

"Conferences offer an important reminder that you are not on your own, which is particularly helpful if there aren't a lot of people at your institution conducting related research. I also find them very helpful for learning about new areas and publications. As a speaker, I am always keen to get feedback from the audience. It is a way of testing out ideas and my thinking before I write a full journal paper."

Kate Sang, associate professor at Heriot-Watt University

continued

To end, two pertinent quotes:

"Attend seminars, forums, conferences, summits and sessions where interesting topics about dream fulfillment and personal branding are prioritized themes and topics. Get exposed to better ways of doing things."

Israelmore Ayivor, "Shaping the Dream"

"Since the 1970s, I've been a big fan of attending conferences as a great way to learn, network, socialize and enjoy a new environment. It's always refreshing to get out and see a whole new world."

Mark Skousen

With these thoughts I wish you happy reading of our new *CRS Newsletter* and a productive year. ■

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1,180

attendees from 42 countries gathered for the Annual Meeting of the Controlled Release Society in Boston, Massachusetts

4

plenary speakers discussed the future of delivery science and technoogy

Robert Langer

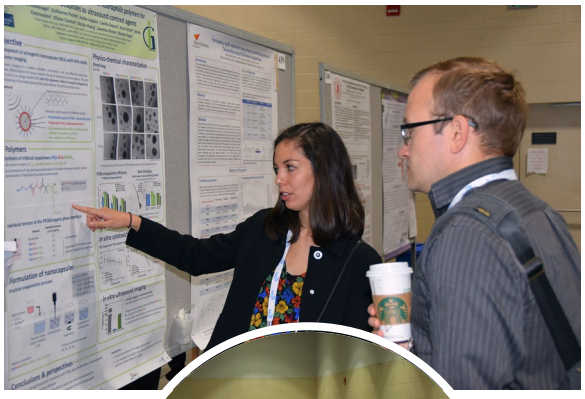
Henry Brem

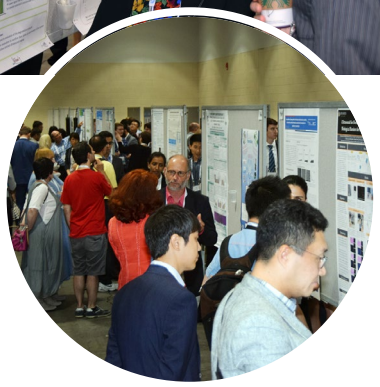
Amar Sawhney

Paula Hammond

551

scientific posters were on display and poster authors shared their research





6

industry-sponsored roundtables inspired thought-provoking discussion

7

students were awarded the Robert Langer Student Travel Grant to attend the 2017 annual meeting

103

oral presenters encouraged discussion through presentations and dialogue

69

exhibitors introduced cutting-edge technology, products, and services

10

students from four CRS Local Chapters were awarded the CRS Local Chapter Young Scientist Travel Grant to attend the 2017 annual meeting

Thank You to the Exhibitors at the 2017 CRS Annual Meeting

This year's theme "Collaborate, Connect, Innovate" brought together a dynamic meeting of the minds in Boston, Massachusetts, with over 65 exhibitors. These organizations support the research and development needs of delivery science and technology with innovative products and services, and they helped make the annual meeting a terrific success. Thank you 2017 CRS exhibitors!

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Advanced Polymer Materials Inc.
Agilent Technologies
Akina, Inc.: PolySciTech Division
American Pharmaceutical Review
Anton Paar USA
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Springer
Surface Measurement Systems
Suven Life Sciences Limited
Teledyne Hanson Research
Texture Technologies
The Medicine Maker
TissueGen Inc.
Ursatec Verpackung GmbH
Wyatt Technology Corporation

"Finding Diamonds on Unpaved Paths": An Interview with Amar Sawhney, a Self-Made Entrepreneur and Leader in the Field of Medical Technology

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

Dr. Amarpreet Sawhney

"There are no diamonds to be found on the well-trodden path," said Dr. Amarpreet Sawhney, a self-made successful entrepreneur and leader in medical technology. He is currently chairman of the board for Ocular Therapeutix, Inc., a public company on the verge of developing multiple products for unmet ophthalmic needs. He also acts as president of Instylla, Inc., chairman of Augmenix, Inc., and serves on the board of directors for Augmenix and Axtria. In his career, he has founded, grown, and sold multiple companies. Previously, he was founder and CEO of Confluent Surgical (acquired by Covidien), chairman of MarketRx (acquired by Cognizant), and technology founder of both Focal Inc. (acquired by Genzyme) and Access Closure Inc. (acquired by Cardinal Health).

A chemical engineer hailing from the Indian Institute of Technology–Delhi, Amar's entrepreneurial journey has been full of excitement, and his success has been the result of overcoming a multitude of professional and personal challenges. His inventions started to get patented when he was a graduate student preparing for his M.S. and Ph.D. in chemical engineering from the University of Texas at Austin. So far he has developed technologies and filed over 120 patents, which led to multiple companies that generated over $3 billion in revenue.

Meeting President Obama at his home in Chicago for Obama's birthday.

Dr. Sawhney has been recognized with several awards, including being named one of the "Champions of Change" and an "Outstanding American by Choice" by President Obama. Some of the other awards in his career include being named one of the "Five Most Innovative Medical Device CEOs" by MassDevice and receiving the MassMedic Best Startup Company award, Frost & Sullivan Product Innovation award, MIT Global Indus Technovator award, Ernst & Young Regional Entrepreneur of the Year award, Mass High Tech All Star award, TiE Star award, University of Texas Outstanding Young Engineering Graduate award, and the Indian Institute of Technology–Delhi Distinguished Alumni award.

Q *Going back to your graduate education days, please tell us how you came up with some of the hydrogel technologies. What was the original application? What was the science behind the development?*

A Before I did my Ph.D., my master's thesis was in prevention of postsurgical adhesions in women following abdominal/pelvic surgery. For that, I worked on poly(lactic-*co*-glycolic acid) (PLGA) based material copolymerized with polyethylene glycol (PEG) to try to make an absorbable sheet that would adsorb in about 14 days to prevent adhesion. However, when we tried these sheets in animals, we found that they were extremely inflammatory in the region, and they gave a strong foreign body response from the acidic burst when they degraded in a short period of time. We decided to modify our approach to create barrier films to get a minimal amount of acidic burst so we could prevent inflammation.

We realized that we needed a different material, and we came up with novel macromers, which were PEG polymers extended with degradable units and terminated with polymerizable end groups. These macromers and the gels formed from them, due to short segments of hydroxy esters extending the PEGs, were much more compatible with tissues. We polymerized these macromers using visible light and formed hydrogels for adhesion prevention. These hydrogels worked extremely well in preclinical models. We were using these polymers at 10% concentration, and only about 5% of the entire chain comprised the degradable part; therefore, the acidic burst was all but eliminated.

I was also doing my Ph.D. work at that time in immuno-isolation of islets of Langerhans for cross-species transplantation to help treat type 1 diabetes. In that project, we were also polymerizing non-degradable versions of these materials in contact with cells to perform the immuno-isolation.

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.

Q *What were the patenting strategies in these research projects? Were they product patents or method patents?*

A The PEG acrylates by themselves were not patentable because they had been described before, although not for the purposes we were using them for and the polymerization techniques we were using. We filed for the method patents for polymerization techniques and microencapsulation methods for cells. The degradable macromers were novel, so we filed for both the composition and the methods patents.

Q *What were some of the polymerization parameters observed that led you to look at these materials being valuable in the real world?*

A The polymerization for the basic materials was happening at ultrafast rates, within a couple of seconds. We would use a visible green laser for a few seconds, and ultrafast polymerizations would result without harming the first cell that was in contact with it. Essentially, we were doing chemistry on living cells, without harming them. This obviously had implications for treatment of local diseases. That was the basis for my first company, Focal Inc., where I was the technology founder. That technology formed the basis of further R&D and helped me invent new technologies, which led to multiple new companies.

Q *At what stage did you realize that your inventions had practical applications and needed to be licensed? Who licensed the initial technologies and later marketed them?*

A We were working closely with clinicians, primarily OB/GYN surgeons, and close to 50 patents were filed. At University of Texas at Austin, we were ready to license the technology. One of the venture capital funds—the Mayfield Fund—approached us since they were starting a company that could use this technology, and then these patents were licensed to Focal Inc. In the process, I moved from Austin, Texas, to Boston, Massachusetts.

Q *Please share your experiences (professional and personal) during the formation of Focal Inc. and the cross-country transition.*

A Looking back, it was a difficult experience in both a professional and personal sense. Austin was an easy town to live and move around in. The pace of life was slower compared with Boston, which was more fast-paced, and I didn't know anybody in Boston at that time. My Ph.D. advisor, Dr. Jeff Hubbell, also took a sabbatical for a year and moved out there, so that was helpful in the transition. I was the first employee at Focal Inc. Mark Levin, who is the cofounder and now managing partner for Third Rock Ventures, was at that time a partner at Mayfield Funds and the first CEO of Focal Inc. and Millennium Pharmaceuticals. He asked me to start the labs and hire people for the R&D work. I didn't know much about either of those things at that time, but through hard knocks and learning, I figured it out and things came together.

At Focal Inc., I was able to deliver on the first product, FocalSeal, the first sealant for lung surgery to be approved by the FDA, but over time it became harder to drive the product development direction there for a variety of reasons. At this point I realized that the frustration was making me view things negatively. After reflecting a little, I realized that I wanted to be a positive and action-oriented person, and so I decided to leave Focal to start my own ventures.

Q *What are some of your key patents?*

A I'll provide a partial list. More broadly, my patents deal with novel materials that can be used to form microcapsules, coat surfaces, and create implantable materials for surgical sealing and adhesion prevention. Some of the patents have to do with drug delivery compositions and methods, some with delivery systems, pre-formed shaped hydrogels for biopsy track closure, femoral puncture closure, tissue marking, spacing, and so on. Some deal with photopolymerized systems and some with two-component-based polymerization chemistries.

Patent Number	Title
6,387,977	Redox and photoinitiator systems for priming for improved adherence of gels to substrates
6,306,922	Photopolymerizable biodegradable hydrogels as tissue contacting materials and controlled-release carriers
6,258,870	Gels for encapsulation of biological materials
5,849,839	Multifunctional organic polymers
9,669,117	Implants and biodegradable tissue markers
9,463,004	Biomaterials for track and puncture closure
8,795,709	Superabsorbent, freeze dried hydrogels for medical applications
8,563,027	Drug delivery through hydrogel plugs
8,512,749	Dehydrated hydrogel precursor-based, tissue adherent compositions and methods of use
6,818,018	*In situ* polymerizable hydrogels

continued

Q *Please tell us about some of the key people who have shaped your professional journey and how those experiences have affected your life.*

A In my professional life, Prof. Hubbell, Dr. C. P. Pathak, and my friend and partner Fred Khosravi have played an important role.

Prof. Hubbell, who was my Ph.D. advisor at the University of Texas at Austin, was a guiding force all along the way and had a seminal role to play in founding the technology and its development, identifying the problems at different stages of the company.

Dr. Chandrashekhar Pathak, post-doc in the lab and an expert chemist in photopolymerization, helped us adapt the rapid prototyping techniques used in photolithography to water-soluble polymers like PEGs. Between us—I, a chemical engineer by training and he, an expert chemist—we were able to come up with these innovative materials.

Induction as a fellow of the AIMBE.

A little later in life, after I left Focal Inc., Fred Khosravi helped me start my own ventures. Fred has been my friend, partner, and mentor at the same time, and together we founded Incept, our holding company.

I have also learned a lot from Mark Levin, another exceptional human being with a lot of business acumen and fund-raising experience.

Q *Please describe some of the challenges you have faced after developing and licensing this technology, leading it to commercial success.*

A After moving from an academic to industrial setting, a new group of industrial experts at Focal Inc. decided to take the technology further; polymerization was performed using visible light, and clinical trials were performed. Unfortunately, the clinical trials showed no efficacy at all, which was disturbing, and that was when they finally turned to me and asked me to solve the problem. It was a simple problem. The polymerization system they had developed to polymerize the low-viscosity materials took about 10 seconds to polymerize. These polymers were applied to the pelvic side wall, and by the time the light was shined the low-viscosity material would drip away, so no material was left in place to polymerize. To solve the problem, I took a small team of people; we made these materials more viscous, stronger, and faster polymerizing. We then tested these materials for applications of surgical sealing in an open-surgery situation instead of looking at laparoscopic cases. This led to the development of the first synthetic surgical sealant approved by the FDA, enabling Focal to go public.

In 1998, Focal Inc. failed clinical trials in the adhesion provision site, and they were not pursuing it any further, so I asked Focal's permission to license out some technologies that I wanted to pursue, as I thought the problems could be fixed. Light polymerization was an issue as well, as we can only polymerize on selective spots where the light fell and shadowing was an issue. The polymerization efficiencies were coming out to be very low with the method of light polymerization. They denied permission to license out these patents, and this was frustrating for me. Ultimately, I left my job at Focal Inc., started all over again in the basement of my house without any financial help, developed the novel chemical-based polymerization (a new chemistry approach based on electrophilic-nucleophilic polymerization using two-component systems), found a patent attorney who would defer his cost for a year, and then filed seven or eight patents. This new approach became much more successful because it was easier to use, manufacturing scale-up of the delivery system was simpler, and it could be used both laparoscopically and in open-surgery situations. We were able to raise capital for my first company, Confluent Surgical, which was later acquired by Covidien. We were able to put all the patents in a holding company structure, Incept Inc., which later formed the basis of multiple companies including Confluent Surgical, Access Closure, Endologix, Augmenix, Ocular Therapeutix, and now Instylla, in Massachusetts. The holding company structure via Incept Inc. was also a seminal innovation that allowed us to come up with companies, leading to many more scientific innovations and applications.

Q *What is your secret for maintaining a positive attitude in life despite the entrepreneurial ups and downs?*

A Looking back at my time at Focal Inc., while I learned a lot and contributed a fair bit to the initial success, toward the end I became extremely frustrated due to the difficult decision-making processes. Despite having no resources, I felt it was best to leave and start afresh. I just had my brain and friends like Fred to give me guidance. I am an optimistic person by nature and decided not to let the circumstances affect me negatively. Fred helped me in finding a patent attorney and even crafting my separation agreement with

continued

Focal Inc. I started my new venture, Confluent Surgical, where we eventually developed Duraseal, the first FDA-approved dural sealant, which is now a standard of care for closing the dural incision following brain surgery in the United States.

In difficult moments, you have to look within yourself and ask "what you do really want to do?" and "what will make you happy?" and not look at the short-term monetary things like an attractive salary and stock options. There will be moments in life when you have to take a thoughtful risk and believe in yourself.

After I left Focal Inc., Fred Khosravi helped me a lot during the difficult times with his advice and suggestions. I also went to a lot of clinicians, some top neurosurgeons who I knew previously, and shared my ideas. Friends and family believing and investing in me went a long way to make me feel comfortable. Also, I didn't have any children at that time, and a little bit of equity that I had from Focal Inc. allowed me to take the risk I did.

At NASDAQ tower, during the ceremony for ringing the closing bell for the market.

Q *Please tell us more about product development learnings with Duraseal.*

A Through multiple years of experience, we were able to set up the right trial designs for Duraseal testing before going into the field. We also learned through experience you can get to the trials faster by making relationships and outsourcing the polymer manufacturing part. At Confluent Inc., we fostered a relationship with Dr. Milton Harris, a well-known name in the field of PEG chemistry, and his company, Shearwater Polymers Inc. This strategic relationship really helped us move forward much more efficiently and allowed us to focus our efforts on product development and clinical trials instead of polymer manufacturing.

Q *Tell us about your family.*

A My father has been a big inspiration for me and my brother Mohanbir, who is a professor at Northwestern University's Kellogg Business School. My father was a self-made entrepreneur as well. He instilled the value of education, work ethic, calculated risk taking, being compassionate about work, and being an effective communicator. All of it allowed me to build teams and people believing in our visions. He took early retirement from the Indian Air Force to start a sheet-metal company in Gandhinagar, which had a burgeoning construction industry. He had no background in construction or sheet metal and initially struggled with the business, but eventually he became successful. That had a big impact on my life and made me realize that one can venture into new fields and, with hard work and persistence, eventually find success.

My wife, Deepika, also has played and continues to play an important role in my life. While I was going through struggling times (after leaving Focal Inc.), she secured her MBA and supported the family, which allowed me to keep pursuing my entrepreneurial journey. She also has a way of ensuring that my feet are firmly planted on the ground.

I have two kids: son Anhad (14) and daughter Priya (12). I make a point to spend a lot of quality time with them. ■


With family in Hawaii.

Biocompatible PDMS-*b*-PMOXA Polymersomes for Cell Type Specific Drug Targeting

Klara Kiene,[a] Susanne H. Schenk, Dominik Witzigmann, and Jörg Huwyler
University of Basel, Switzerland

Introduction

Many promising therapeutic compounds suffer from disadvantages such as low bioavailability, rapid clearance, and high systemic toxicity. To overcome these challenges, nanoparticles such as polymersomes can be used as promising drug delivery systems. Polymersomes are vesicles formed by self-assembly of amphiphilic block co-polymers such as poly(dimethylsiloxane)-*b*-poly(2-methyloxazoline) (PDMS-*b*-PMOXA). PDMS-*b*-PMOXA is a promising block co-polymer because the individual polymer blocks have been reported to be biocompatible.

Herein, we present the formulation of polymersomes based on PDMS-*b*-PMOXA, and we demonstrate slow drug release of incorporated model drug (i.e., carboxyfluorescein, CF) *in vitro*. In addition, we focus on the surface modification of PDMS-*b*-PMOXA polymersomes (PP) for targeted drug delivery to hepatocytes. Potential toxicity of the resulting polymersomes is assessed *in vitro* and *in vivo*.[1]

Experimental Approach and Results

PP were prepared by thin-film rehydration and subsequently modified to obtain targeted vesicles (Fig. 1). All PP variants were routinely analyzed by dynamic light scattering (DLS) for average size and size distribution (Table 1). The different modifications resulted in monodisperse suspensions of particles with hydrodynamic diameters of around 150 nm. Cryo-transmission electron microscopy (cryo-TEM) confirmed size and vesicle morphology (Fig. 2A). The polymersomes could be stored in Dulbecco's phosphate-buffered saline (DPBS) at 4°C for at least 4 months without significant change in particle size and polydispersity index (PDI) and without loss of functionality as confirmed by cellular uptake experiments. In addition, the integrity of the particles was tested under forced stress conditions. Unmodified PP were incubated

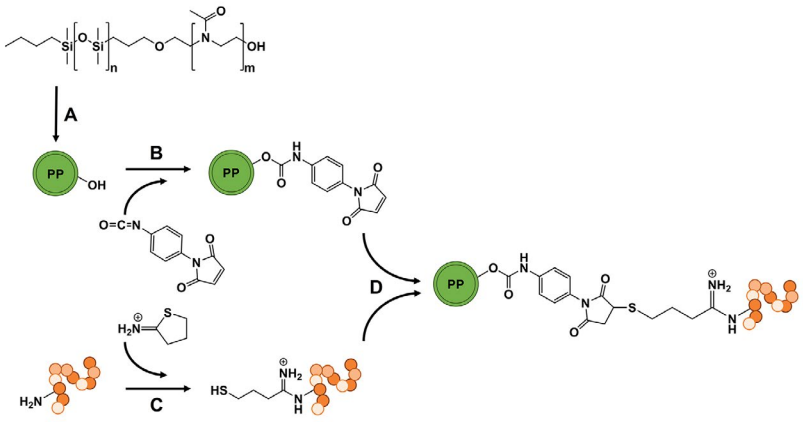

Figure 1. *Preparation of AF targeted PP. (A) Formulation of PP using the thin film rehydration method. (B) Modification of the polymersomes' surface using p-maleimidophenyl-isocyanate to obtain maleimide-functionalized PP and (C) in parallel thiolation of AF using 2-iminothiolane (Traut's activation). (D) Finally, maleimide-functionalized PP and activated AF were covalently linked via Michael addition to achieve PP-AF.*

Table 1. Size and Size Distribution of PDMS-*b*-PMOXA Based Polymersomes[a]

Abbreviation	Full Name of Polymersomes	Diameter (nm)	PDI
PP	PDMS-*b*-PMOXA polymersomes	156.9 ± 8.8	0.082 ± 0.041
PP-F	PP modified with fetuin	155.4 ± 15.0	0.097 ± 0.015
PP-AF	PP modified with asialofetuin	149.8 ± 7.9	0.103 ± 0.019
PP-488	PP modified with HiLyte Fluor 488	161.3 ± 10.2	0.175 ± 0.057
PP-F-488	PP modified with HiLyte Fluor 488 labeled F	148.4 ± 6.3	0.098 ± 0.039
PP-AF-488	PP modified with HiLyte Fluor 488 labeled AF	149.3 ± 1.5	0.098 ± 0.027
PP-CF	PP loaded with CF	155.9 ± 17.5	0.133 ± 0.034

[a] Hydrodynamic diameters (DLS-intensity peaks) and polydispersity index (PDI) of different polymersome formulations were measured by DLS. Data represent mean values ± SD (n = 5). Abbreviations used for the different formulations are indicated.

continued

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Adapted from Kiene et al. (https://doi.org/10.1016/j.ejpb.2017.07.002)[1] with permission from Elsevier.

in DPBS, 3% bovine serum albumin (BSA), or 50% fetal calf serum (FCS) for 7 days at 37˚C. As outlined in Figure 2B, no statistically significant changes in particle diameters occurred over time. To demonstrate that PDMS-*b*-PMOXA forms tight vesicles, we encapsulated CF as a model drug into PP and subsequently measured CF release into DPBS at different temperatures over 96 h using a microdialysis device (Fig. 2C). CF release was temperature dependent and occurred in a slow and sustained manner over a long period of time. No initial burst release was observed at any of the tested temperatures, and no plateau was reached within the duration of the experiment. Moreover, a similar release profile was observed in buffers containing naturally occurring serum proteins (3% BSA and 50% FCS, observation period 48 h). Using the standard thin-film rehydration method, the achieved loading capacity was 1.5 ± 0.2 nmol of CF per mg of PP. This seems low. However; to achieve therapeutic effects, alteration of pharmacokinetics is the most important factor. Nanoparticles can shift the balance in off- and on-target accumulation. Therefore, already a low percentage of nanoparticles delivered to the diseased tissue may offer a benefit to the patients by reducing severe side effects of encapsulated drugs.[2]

For hepatocyte-specific targeting, we selected the asialoglycoprotein receptor (ASGPR),[3] and its naturally occurring ligand asialofetuin (AF) was covalently linked to PP (PP-AF). Using confocal microscopy and flow cytometry (FACS), we showed receptor-mediated and energy-dependent uptake of PP-AF by the hepatocarcinoma cell line HepG2 (Fig. 3).

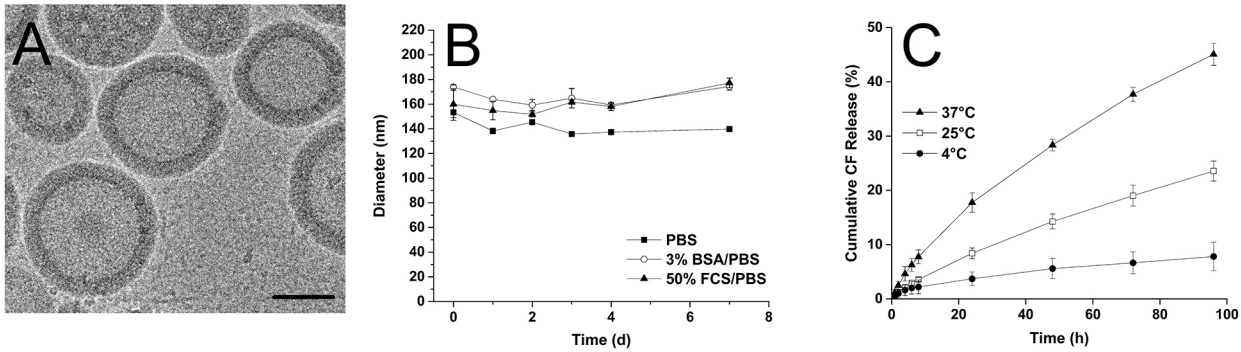

Figure 2. *Characterization of PP. (A) Cryo-TEM analysis of PP showed the formation of hollow spheres. Scale bar = 100 nm. (B) Stability of PP in different buffers at 37˚C. Changes in hydrodynamic diameters were measured by DLS. Values are means ± SD (n = 3). (C) Cumulative release profile of CF from PP-CF in DPBS measured at different temperatures. SD is shown with error bars (n = 3).*

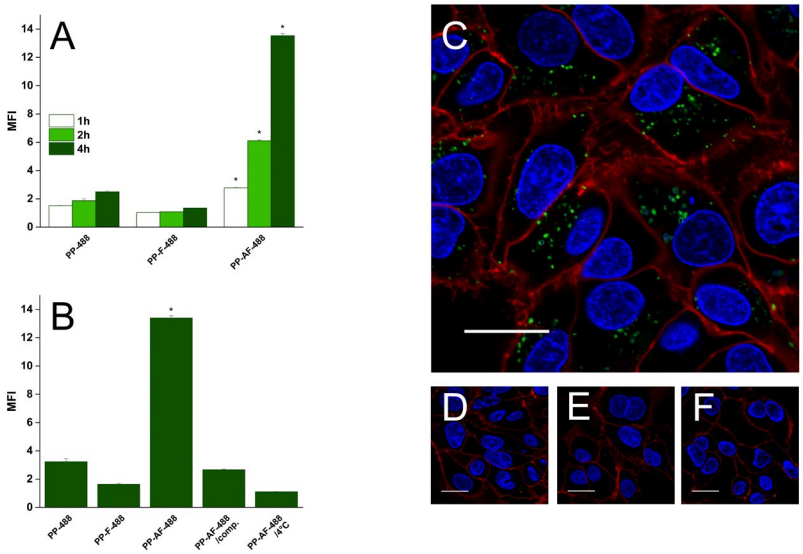

Figure 3. *Time-dependent and receptor-specific cellular uptake of targeted PP. (A) HepG2 cells were incubated with PP-488, PP-F-488, and PP-AF-488 and analyzed by FACS to quantify uptake of the differently modified PP. Mean fluorescence intensity (MFI) was normalized to untreated control cells. SD is shown with error bars (n = 3); asterisk (*) indicates P < 0.01. (B) ASGPR specific uptake of PP-AF-488 by HepG2 cells. PP-488 (negative control) and PP-AF-488: cells were incubated with the indicated polymersomes for 4 h at 37˚C. PP-AF-488/comp: for competitive inhibition, cells were pre-incubated for 1 h with an excess of free AF before adding PP-AF-488. PP-AF-488/4˚C: HepG2 cells were incubated at 4˚C in the presence of PP-AF-488. Uptake determined by FACS is shown as MFI normalized to untreated control cells. SD is shown with error bars (n = 3); asterisk (*) indicates P < 0.01. (C–F) Confocal microscopy after 4 h uptake of respective polymersomes. Nuclei are blue, cell membranes red, and PP-488 and PP-AF-488 green. Scale bar = 20 µm. (C) PP-AF-488. (D) PP-488. (E) PP-AF-488/comp. (F) PP-AF-488/4˚C.*

continued

To confirm the biocompatibility of various PP formulations *in vitro*, we performed MTT assays. For all concentrations and formulations, cell viability was at least 80% (Fig. 4A). To investigate whether our polymersomes exhibit adverse effects *in vivo,* we used zebrafish embryos (ZFE). This vertebrate model is becoming increasingly recognized as an "intermediate" model for toxicity screening of small molecules but also nanoparticles before turning to experiments in rodents.[4] ZFE with chorion as well as dechorionized ZFE were exposed up to 96 h postfertilization (hpf) to the highest concentration of different PP formulations that were non-toxic *in vitro* (500 µg/mL). As a result, no signs of developmental toxicity were observed during the whole experiment (equal hatching rate, no malformations such as pericardial edema or tail malformations), suggesting good biocompatibility of all PP variants (Fig. 4B–D). In addition, preliminary experiments indicate that even direct injection of our polymersomes into the blood circulation of 72 hpf ZFE (using a microinjection device) did not result in acute toxicity. We conclude from these experiments that our polymersomes are well tolerated within a typical dose range suggested for use of nanomedicines.[5]

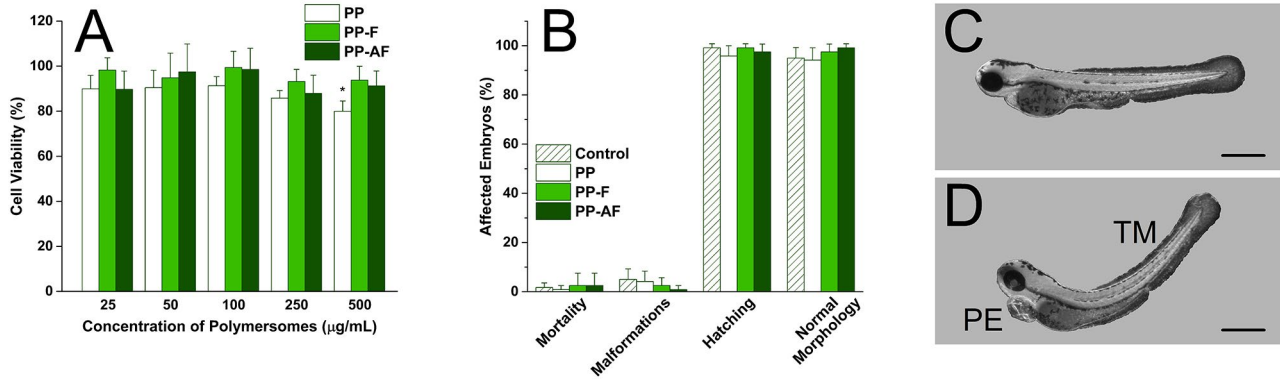

Figure 4. *In vitro and in vivo toxicity. (A) MTT-assay. Cell viability of HepG2 cells after incubation for 24 h with increasing concentrations of differently modified PP. Cell viability of untreated control cells is 100%. SD is shown with error bars (n = 8); asterisk (*) indicates P < 0.01. (B) Toxicity of differently modified polymersomes in zebrafish (96 hpf). Percentages of mortality in the early zebrafish larvae, larvae affected by morphological malformations, hatching rate, and larvae with normal morphology are shown. The polymersome formulations were tested and compared to control (no polymersomes). Values are means ± SD (n = 30). (C, D) Representative images of ZFE 96 hpf. (C) ZFE with normal morphology. (D) Exemplified ZFE with malformations (PE pericardial edema, TM tail malformation). Scale bar = 0.5 mm.*

Conclusion

In conclusion, we achieved a targeted drug delivery system that is biocompatible *in vitro* and presumably also *in vivo*. It could be loaded with a hydrophilic model compound, and sustained release over a long time was achieved in DPBS as well as in serum protein containing media. Successful AF conjugation and therefore effective ASGPR targeting make our polymersomes a promising tool for clinical application in the field of liver disorders.

Acknowledgements

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Revisiting the Use of sPLA$_2$-Sensitive Liposomes in Cancer Therapy

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It is still a pending issue for many "smart" nanocarriers endowed with a controlled and site-specific drug release mechanism to overcome the therapeutic efficacy and minimize therapy-associated side effects obtained by their older brothers, the golden benchmarked non-sensitive formulations. Motivated by current clinical development stage of enzyme-sensitive systems, in particular of phospholipase A2 (sPLA$_2$)-degradable formulations, we aim in the present work to revisit the potential use of sPLA$_2$-sensitive liposome formulations of platinum drugs, here oxaliplatin (L-OHP), and to get a deeper insight into the sPLA$_2$ dependency of previous developed formulations, understanding the therapeutic window that is obtainable with such formulations. We report here L-OHP loaded liposomes with low or high sensitivity toward sPLA$_2$-triggered degradation as drug delivery nanocarriers, and we compare these slow- and fast-releasing formulations to non-sensitive nanocarriers, assessing their *in vitro* cytotoxicity against cultured cancer cells, as well as their efficacy and tolerability *in vivo* in mice bearing human tumors. A graphical abstract is presented as Figure 1.

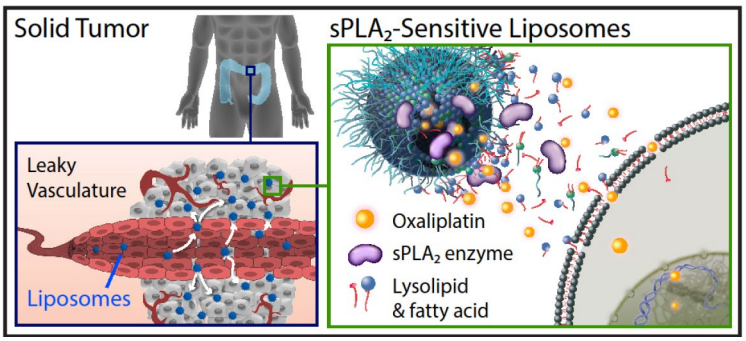

Figure 1. *Graphical abstract.*

The enzymatic activity of sPLA$_2$ toward liposome degradation and consequently release of their cargo can be significantly modulated by the composition of the lipid bilayer and its morphological and physicochemical properties. This was demonstrated in *in vitro* release studies using calcein as a drug surrogate at self-quenching concentrations loaded within the different liposome carriers. We show that the molar ratio of negatively charged lipid present in the liposome membrane played a key role in the enzyme activity evaluated from calcein release profiles (Fig. 2A). In membranes composed of DPPC/DPPG/DSPE-PEG2k, when 25% of the negatively charged lipid DPPG was present in the bilayer (DP(25)), only the sPLA$_2$ from tears was able to cause partial calcein release, whereas increasing the percentage of DPPG lipid to 40% (DP(40)), the membrane became fully enzyme-degradable and calcein was completely released within 1,500 s irrespective of the source of enzyme (sPLA$_2$ in human tears = 19.3 μg/mL;

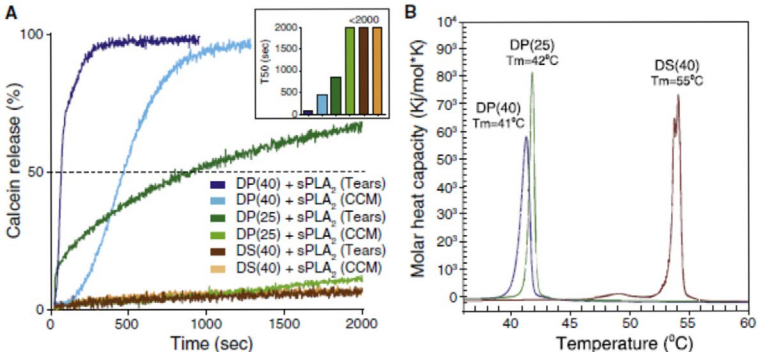

Figure 2. *Calcein release profiles and phase transition diagrams of liposome formulations. (A) In vitro sPLA$_2$-dependent release kinetics of calcein from liposomal formulations incubated at 37°C.* Human tear fluid and cell conditioned media *(CCM) from human Colo205 cancer cells were used as enzyme sources of sPLA$_2$. All results are expressed relative to 100% release observed after addition of Triton X-100. Results are representative of at least three experiments. Inset shows the time-intersect for the individual formulations reaching 50% release (T50) in seconds. (B) DSC endotherms highlighting the main phase transition temperature (Tm) of the different formulations. Abbreviations: DP(25) = DPPC/DPPG/DSPE-PEG2k (70:25:5 mol%); DP(40) = DPPC/DPPG/DSPE-PEG2k (55:40:5 mol%); and DS(40) = DSPC/DSPG/DSPE-PEG2k (55:40:5 mol%).*

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Adapted from Pourhassan et al. (https://doi.org/10.1016/j.jconrel.2017.06.024)[1] with permission from Elsevier.

$sPLA_2$ in cell conditioned media (CCM) = 185.4 ng/mL).[1] DSC of the formulations (Fig. 2B) showed that liposomes made of 16-carbon chain lipids (DP(25) and DP(40)) have an overall main phase transition temperature (Tm) of 41 and 42°C, respectively, and were highly sensitive toward $sPLA_2$ degradation, whereas in 18-carbon lipid membranes (DS(40)) with higher Tm of 55°C, the enzyme activity was almost abolished, which can be explained by its reduced access to the cleavable region in the membrane owing to its gel state behavior. This was evident from the time it took to reach 50% release (T50) of calcein with DP(40) liposomes (70.1 s) being >10 and >30 times faster than DP(25) liposomes (857.7 s) and DS(40) liposomes (>2,000 s), respectively (Fig. 2A, inset).

Efficient $sPLA_2$-dependent growth inhibition of colorectal cancer cells was demonstrated *in vitro*. The antiproliferative capacity of free L-OHP and L-OHP loaded in sensitive DP(25) or DP(40), and in non-sensitive (stealth) formulations were tested by MTS assay in $sPLA_2$-secreting Colo205 cell line and in non-secreting HT-29 cells with added exogenous $sPLA_2$ using cell CCM from Colo205 cells as a source of enzyme (Fig. 3). In concordance with the liposome sensitivity of $sPLA_2$ shown in Figure 2A, efficient growth inhibition of $sPLA_2$ non-secreting HT-29 cells was only observed when the liposomes became activated by exogenous $sPLA_2$ (Fig. 3A). In both colorectal cancer cell lines $sPLA_2$-sensitive liposomal L-OHP were highly cytotoxic, with drug concentrations able to inhibit cell growth by 50% (IC50) around 10–12.5 μM (Fig. 3B). In addition, the degree of growth inhibition of HT-29 cells induced by the liposomes followed the sensitivity of the formulations toward $sPLA_2$ hydrolysis (Fig. 3B). In control experiments in which HT-29 cells were treated in the absence of $sPLA_2$ (without Colo205 CCM), the sensitive liposomes showed similar antiproliferative profiles as the non-degradable stealth formulation.[1] Taken together, these findings illustrate an efficient and stable formulation of L-OHP in enzyme-sensitive liposomes that carry a desirable controlled release mechanism based on $sPLA_2$-mediated activation.

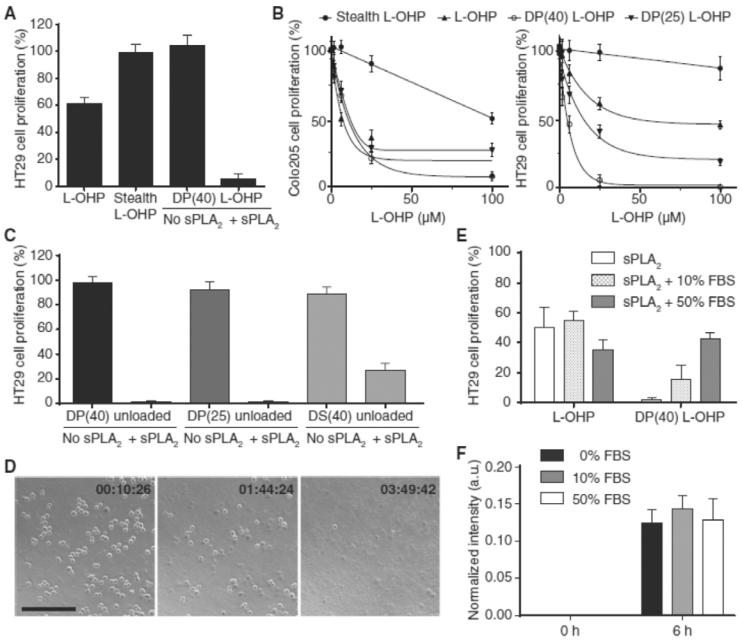

Figure 3. *In vitro evaluation of the $sPLA_2$-sensitive concept. (A) Lack of cytotoxicity of $sPLA_2$-sensitive liposomes against non-$sPLA_2$-secreting HT-29 cells in the absence of exogenous $sPLA_2$ shows the specificity of the concept toward $sPLA_2$ and dependence of $sPLA_2$ activation. (B) In vitro cytotoxicity of L-OHP in free form or encapsulated in $sPLA_2$-sensitive liposomes (DP(25) and DP(40)) or in non-degradable liposomes (stealth) tested against $sPLA_2$-secreting Colo205 cells and $sPLA_2$-deficient HT-29 cells in the presence of Colo205 cell conditioned medium (CCM) containing $sPLA_2$. (C) Cytolytic activity of unloaded (without L-OHP) $sPLA_2$-sensitive liposomes arise from cellular lysis as a consequence of $sPLA_2$-driven hydrolysis and formation of permeability enhancing/membrane lysing components. (D) Time-lapse micrographs of HT-29 cells following 3 h of incubation with DP(40) in the presence of $sPLA_2$-proficient Colo205 CCM. (E) Inhibitory effect of $sPLA_2$-sensitive liposomes on HT-29 cell proliferation is modulated by presence of serum components. (F) Effect of serum (10–50% FBS) on the enzymatic activity of $sPLA_2$. Results are triplicates from one experiment (mean ± SD) and representative of three independent experiments. Abbreviations: L-OHP = oxaliplatin; DP(25) = DPPC/DPPG/DSPE-PEG2k (70:25:5 mol%); DP(40) = DPPC/DPPG/DSPE-PEG2k (55:40:5 mol%); and DS(40) = DSPC/DSPG/DSPE-PEG2k (55:40:5 mol%); stealth = HSPC/Chol/DSPE-PEG2k (57:38:5 mol%).*

Because a triggered release strategy based on $sPLA_2$ activity is known to generate permeability-enhancing lysolipids and fatty acids, we investigated their contribution to the cytotoxic effect by measuring the growth inhibition of HT-29 cells treated with unloaded $sPLA_2$-sensitive liposomes with and without added $sPLA_2$ (Fig. 3C). For HT-29 cells, both the DP(25) and DP(40) formulations were able to induce complete growth inhibition of the tumor cells at both molar ratios of the PG lipid in the membrane investigated, whereas the DS(40) formulation only induced partial growth inhibition despite the presence of 40% PG. Time-lapse micrographs of HT-29 cells during treatment with unloaded DP(40) liposomes and $sPLA_2$-containing CCM revealed that the observed efficient growth inhibition was in effect owing to the complete disruption of the cellular membranes (Fig. 3D). Thus, based on the evidence from the calcein release experiments and the *in vitro* cytotoxicity, $sPLA_2$-sensitive liposomes were confirmed to act as efficient prodrugs, in which their *in vitro* antitumor efficiency was primarily owed to the generation of cell-permeable byproducts from the action of the enzymatic hydrolysis.

Serum albumin has previously been shown to bind up to five lysophospholipids per albumin molecule,[2] and therefore the presence of high amounts of plasma proteins is expected to strongly modulate the permeability-enhancing properties of these components, and conversely thereby affect the effective cell lytic activity of $sPLA_2$-sensitive liposomal carriers as well. For this reason, to address the effect of serum on the anti-proliferative effect of $sPLA_2$-sensitive liposomes, HT-29 cells were treated with $sPLA_2$-sensitive liposomal L-OHP together with Colo205 CCM in the absence of serum or spiked with 10% (low) or 50% (high)

continued

fetal bovine serum (Fig. 3E). We demonstrate that high levels of serum proteins eliminate the cytotoxic effect of the carrier. These results support that the *in vivo* cytotoxic potential of generated permeability-enhancing products will not only depend on the intratumoral lipid concentration but also on the concentration of various plasma proteins present in the interstitial compartment of the cancer. Additionally, to rule out that the presence of serum affects the enzymatic activity of $sPLA_2$, we measured the amount of lysolipids generated after treatment of $sPLA_2$-sensitive liposomes with enzyme in the presence of serum using mass spectroscopy. The level of lysoPPG generated was found to be unchanged from DP(40) liposomes in the presence of serum (Fig. 3F). This demonstrates that even though components in serum can sequester the generated permeability-enhancing components from $sPLA_2$-sensitive liposomes, the encapsulated drug is released as $sPLA_2$ hydrolyzes the liposomes, irrespective of the presence of serum proteins. Of course, this process is further complicated by the presence of lipase inhibitors in a clinical setting, a feature not readily captured and accounted for here by using murine and bovine serum models.

Previous findings have shown that several inbred mouse strains have an intact murine group-II $sPLA_2$ gene, which raises the likelihood of background $sPLA_2$ levels being present in the NMRI nude model used herein, even though the grafted tumor cells do not secrete the $sPLA_2$ enzyme.[3] We first evaluated the efficacy and tolerability of L-OHP formulated in $sPLA_2$-sensitive liposomes in a dose escalation study in NMRI nude mice bearing non-$sPLA_2$-secreting FaDu squamous carcinoma. This was done to determine the baseline of the antitumor efficacy of these particle systems in a tumor model that lacked the capacity of stimulating specific drug release and, furthermore, to establish the maximum tolerated dose including any potential unforeseen side effects occurring from premature activation by murine phospholipases. The mice received 6 i.v. doses of 4 or 8 mg/kg every 4 days, with the first dose administered upon the tumors reaching 50 mm^3 in size. L-OHP formulated in DP(40) liposomes at 4 mg/kg was able to induce a minor increase in tumor growth reduction compared with mice receiving free L-OHP at equimolar doses, reaching an equivalent response rate as twice the amount of free drug injected; however, this was only a moderate effect (Fig. 4A). In turn, the low antitumor effect did not give rise to an increase in survival rates (Fig. 4B). Increasing the dose of L-OHP formulated in DP(40) liposomes to 8 mg/kg (equivalent to a lipid dose of 113 mg/kg) was poorly tolerated and led to petechial cutaneous hemorrhages in the skin of the mice,[1] along with concurrent weight loss (Fig. 4C) and dehydration requiring immediate euthanasia. At this high dose, DP(40)-treated mice showed severe signs of toxicity and poor tolerance late in the course of treatment suggestive of a cumulative effect, with 3 out of 8 mice displaying massive weight loss 4 days after second and third injections, and 5 out of 8 mice presenting severe cutaneous bleedings following 4 days after the second treatment. In contrast, at 4 mg/kg the mice showed no signs of toxicity from neither DP(25) nor DP(40), with 8 out of 8 mice reaching the humane endpoint of tumor burden.

Continued expression of $sPLA_2$ by human Colo205 colorectal carcinoma cells following implantation in mice has previously been established[4] and was confirmed here.[1] This allowed us to use Colo205 xenografts, as a $sPLA_2$-proficient human cancer model with an elevated tumor expression profile of $sPLA_2$ and sensitivity toward L-OHP were therefore expected to serve as a suitable experimental model to evaluate the *in vivo* performance of the present enzyme-responsive formulations. Here we determined the efficacy of 4 i.v. injections of L-OHP in mice implanted with ectopic Colo205 tumors at 5 mg/kg administered every 4 days, as either unencapsulated drug or formulated in liposomes with a high degree of $sPLA_2$ sensitivity (DP(40)), low sensitivity (DP(25)), and non-sensitive highly stable liposomes (stealth) (Fig. 4D–F). In comparison to FaDu tumors, Colo205 xenografts did exhibit marginally higher response rates toward free L-OHP following three intravenous injections. Although for the liposomal formulations of L-OHP, despite a minor increased growth-inhibiting effect relative to the free drug, encapsulating L-OHP within $sPLA_2$-sensitive liposomal formulations did not improve the antitumor effect compared with non-sensitive liposomes (Fig. 4D and E). In fact, all of the tested formulations

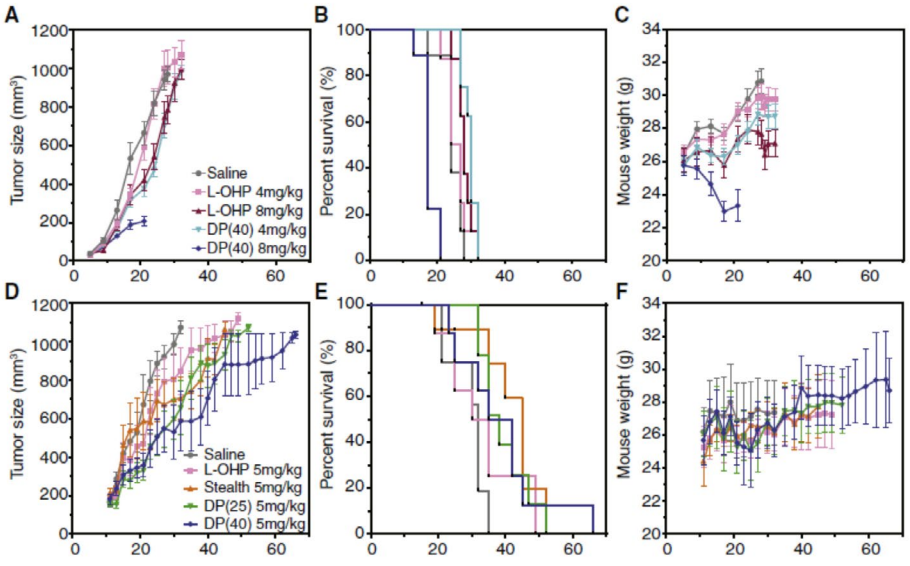

Figure 4. *Therapeutic efficacy of $sPLA_2$-sensitive formulations in female nude NMRI mice bearing FaDu tumors with no $sPLA_2$ expression (upper panel) and Colo205 tumors with high $sPLA_2$ expression (lower panel). In FaDu xenografts, mice received 6 i.v. injections every 4 days (6q4d) of 4 or 8 mg/kg L-OHP free or loaded in highly $sPLA_2$-sensitive DP(40) liposomes. Colo205-bearing mice received 4 i.v. injections every 4 days (4q4d) of 5 mg/kg L-OHP free or loaded in liposomes with varying degree of sensitivity toward $sPLA_2$ (high, DP(40); low, DP(25); non, stealth). (A, B) Mean tumor volumes. (B, E) Kaplan-Maier survival plots based on specified humane end points. (C, F) Animal body weights.*

continued

exhibited >45% treatment-to-control ratios (%T/C) and were therefore statistically therapeutically inactive. No significant (*P* values > 0.05) increase in survival proportions between the different treatments was obtained in the Colo205 model, as were assessed by the median survival of the groups (Fig. 4E). A summary of the parameters from the Colo205 efficacy study is presented herein.[1]

With respect to the tolerability of the formulations, 2 out of 9 mice bearing Colo205 xenografts receiving four injections of a reduced dose of 5 mg/kg of DP(40) continued to display signs of poor tolerance and experienced excessive weight loss during the course of treatment (4 days after third injection and 2 days after the fourth injection, respectively). The less sensitive DP(25) formulation was on the other hand well-tolerated, with none of the mice displaying systemic toxicity and not accompanied by any weight loss (Fig. 4F). Consistent with the observations in the dose-escalation study, a schedule of multiple injections at a reduced dose of 5 mg/kg (equivalent to a lipid dose of 50 mg/kg for DP(25) and 58 mg/kg for DP(40), respectively) did not cause hemorrhaging in the skin of treated mice. We therefore suspect that the hemorrhages found in the skin are caused by an excessive extravasation of the particles into the skin of the mice when administering multiple large doses, subsequently leading to an activation of the particles by host $sPLA_2$ present in the skin, where it plays an intricate role in maintaining the integrity of the epidermis.[5] However, further investigations are needed to address whether or not this diffuse bleeding is also implicated in the mortality of the animals.

These results clearly demonstrate the inability of using the highly sensitive DP(40) formulation at effective tumor growth-inhibiting doses owing to dose-limiting systemic toxicities. Conversely, lowering the sensitivity of the particles toward $sPLA_2$, as seen with DP(25), the formulation becomes well-tolerated yet is therapeutically inactive and indistinguishable from liposomes not carrying enzyme-triggered release properties. The latter presumably being from a lack in ability to become hydrolyzed inside the tumor to a significant extent.

To establish the underlying cause of toxicity of the DP(40) formulation, histological examination was conducted on the liver of the mice. The principal cause of death was determined to be owing to multifocal peracute hepatonecrotic lesions. Analyzing the liver of a mouse treated with a single high dose of 10 mg/kg of DP(40) showed no signs of liver damage 4 days after treatment (Fig. 5A), whereas following 3 injections of 8 mg/kg every 4 days necrotic lesions became apparent in the liver (Fig. 5B). This illustrates that the cumulative accumulation of the liposomes in the liver causes the toxicity produced in the organ and, thus, to the animal. On the other hand, these signs were not observed in mice treated with low $sPLA_2$-sensitive (DP(25)) and non-degradable liposomes (stealth) (data not shown), despite it being well-known that PEGylated liposomes do accumulate in the liver to a high extent. Therefore, we believe the liver damage arises from the combined effect of high liver accumulation of the liposomes along with a high $sPLA_2$ degradability. Because elevated levels of this enzyme are produced by hepatocytes,[6] we speculate that activation of these particles from the action of hepatic $sPLA_2$ does occur for the DP(40) formulation, resulting in the release of the encapsulated drug, and at the same time high local concentrations of permeability-enhancing components are formed, creating the observed degenerative condition. In addition, the secretion of $sPLA_2$ into the hepatic intercellular space is further exacerbated following drug-mediated injury of the hepatic cells, which can then further deteriorate the breakdown of the tissue in a self-perpetuating and vicious cycle.[7]

Taken together, these data illustrate that $sPLA_2$-mediated controlled release from liposomal drug carriers, investigated here for delivering the platinum drug L-OHP, appears to preclinically have a self-limiting effect on the antitumor efficacy by causing inadvertent liver toxicity following systemic administration. The main limitation of this system, therefore, is the release of membrane-active lysophospholipids and free fatty acids driven by hepatic enzymatic hydrolysis, which in particular affects the usage of highly sensitive liposome formulations designed to facilitate fast local drug release inside tumors but more so hampers the dosage required to attain therapeutic efficacy.

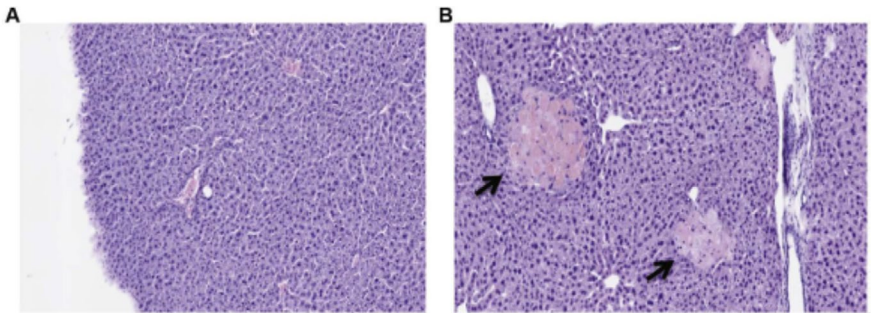

Figure 5. *Histological examination of liver after single or multiple dosings of highly $sPLA_2$-sensitive liposomal L-OHP. (A) No damaged regions were observed in the liver 4 days after a single injection of DP(40) at 10 mg/kg. (B) Necrotic manifestations (arrows) in the liver following three injections of 8 mg/kg of DP(40) administered every 4 days. Multiple injections of high-$sPLA_2$-sensitive DP(40) formulations result in multifocal peracute hepatonecrotic lesions. Staining was performed with hematoxylin and eosin.*

In conclusion, we did not find evidence that increased drug efficacy could be obtained by using a $sPLA_2$-triggered drug release mechanism with high sensitivity, compared with low- or non-sensitive liposomes. In contrast, our findings suggest that $sPLA_2$-responsive liposomes instead pose a risk of systemic toxicity from a combined effect of both their sensitivity toward the enzyme and the additive up-concentration of dosed particles accumulating in the liver following repeated dosage. Increasing the amount of PG in the liposome membranes to 40% in order to reach a high rate of drug release also increased the incidence of systemic toxicity and restricted their

continued

use for *in vivo* applications, whereas with 25% PG, despite no detectable systemic toxicity in our preclinical model did not produce higher growth inhibition relative to non-degradable PEGylated liposomes.

Overall, the $sPLA_2$-induced drug release strategy suffers from a narrow therapeutic window, in which $sPLA_2$-sensitive liposomes are limited by drug-related liver failure, whereas low-sensitive formulations, such as the clinically used LiPlaCis®, lack an actively $sPLA_2$-controlled released mechanism, thus behaving therapeutically as conventional non-degradable PEGylated formulations. This raises concerns as to whether LiPlaCis® and similar formulations using $sPLA_2$ as a target can benefit cancer patients.

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Porosity, Water Permeation, and Mechanisms of Release from Solid Lipid Matrices

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Solid lipid excipients are widely used in the formulation of controlled and modified release (CR/MR) oral and parenteral dosage forms,[1,2] in which they function as matrices, binders, and fillers. In contrast to other CR/MR excipients, such as high-molecular-weight polymers (e.g., methyl cellulose), solid lipid excipients exhibit a high degree of hydrophobicity, which allows them to function as low-porosity, water-impermeable barriers. When used in combination with the appropriate release rate modifiers, solid lipids enable a wide range of release rates, from minutes to months, as exemplified in a number of published works.[2,3]

Bend Research, now a part of Lonza, has developed a lipid multiparticulate (LMP) platform technology using the melt–spray–congeal process. This platform involves suspending crystalline active pharmaceutical ingredient (API) in a melt of lipid excipients, which is then fed onto a spinning disc atomizer to produce drug-containing microspheres. API release from LMP microspheres can be modulated via particle size and the loading of water-soluble release modifiers. Additionally, LMPs can be coated for taste masking or enteric release applications.

Rational selection of lipid excipients for LMPs requires consideration of certain physical properties such as melting point, chemical composition and impurities, hydrophilic/lipophilic balance, and crystal polymorphism. These properties help formulators to optimize compatibility with the API and other excipients, as well as optimize the physical and chemical stability of the intermediate or dosage form.

The use of lipid excipient properties to parameterize and guide release rate models is an active area of study. Mechanisms of release from binary crystalline lipid–drug mixtures under *in vitro* conditions are proposed to proceed by two possible rate-limiting steps: initial wetting and water permeation into the particle versus diffusion-limited flux of API out of the particle. Several forms of diffusion-limited release mechanisms have been proposed, including empirically parameterized through-particle diffusion,[3] diffusion through a water-filled porous network,[4] and diffusion-limited wetting of the particle.[5] Diffusion pathways may involve grain boundaries of crystalline lipids, boundaries with crystalline APIs, hydrated lamellae, osmotic wicking, or diffusion through the lipid crystallites themselves. The difficulties in distinguishing between the diffusional rates of initial wetting and hydration versus porous diffusion of API out of a particle have been recognized.[3]

The goal of this work is to understand the functionality and relevant physical properties of lipid excipients that impact *in vitro* dissolution performance. Given that either initial water permeation into the microparticle or diffusion-controlled release of API out of the particle could be rate limiting steps, 1) how does one distinguish between these two cases and 2) what role do the intrinsic properties of the lipid matrix and the presence of embedded crystalline API play in these mechanisms? Toward addressing these questions, API release and wetting properties of stearyl alcohol, glycerol mono/di/tribehenate (20/50/30, hereafter referred to by its commercial name, Compritol 888 ATO), and beeswax were investigated both as pure ingredients and in binary mixtures using crystalline caffeine at a 30% loading.

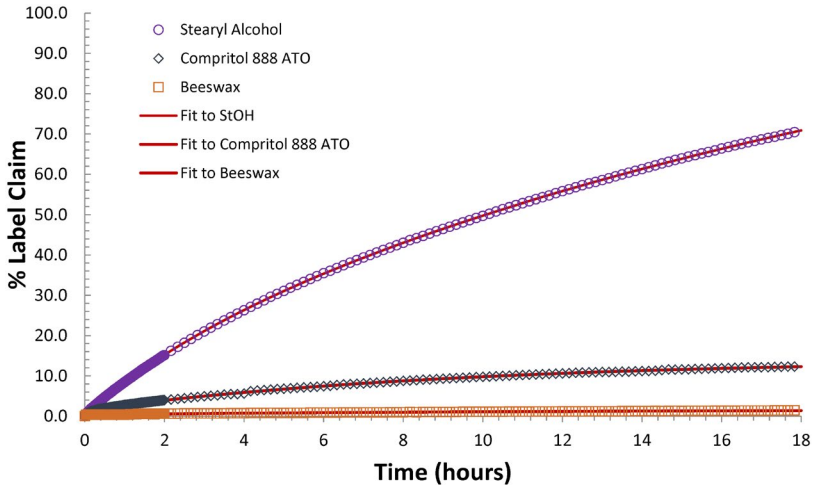

Figure 1. *USP-2 dissolution (pH 6.2 10 mM phosphate) of 3 mm pellets of 30% w/w caffeine in stearyl alcohol, Compritol 888 ATO, or beeswax. Solid red lines are bi-exponential fits to the data, %release = $y_0 + A_1e^{-k1t} + A_2e^{-k2t}$.*

Figure 1 shows dissolution profiles for caffeine formulated with stearyl alcohol, Compritol 888 ATO, and beeswax matrices in the form of ~3 mm pellets. Initial rates of release from these particles rank the order as stearyl alcohol > Compritol 888 ATO > beeswax. Fitting of the release profiles indicates complex kinetic behavior: biphasic kinetics and incomplete release for slower matrices at infinite time. As elaborated

continued

below, these release profiles are interpreted as being rate limited by movement of the wetting front into the particle followed by porous diffusion of API out.

Surface wetting kinetics within this series were probed using dynamic contact angle measurements of water on thin films of these lipids. Figure 2 shows that stearyl alcohol exhibits a fast decrease in contact angle over the first 5 min of measurement, indicating favorable wetting. Compritol 888 ATO and beeswax show evidence of less favorable wetting with a slower reduction in their contact angles over time, which do not decrease below 90° by the end of the measurement. These results suggest the potential for slow water permeation through two of the lipid matrices within this series, with possible rate limiting impacts on API release. Because these measurements were confined to the first 300 s of wetting and can be influenced by surface roughness, nuclear magnetic resonance (NMR) spectroscopy was employed to perform permeation observations on longer timescales.

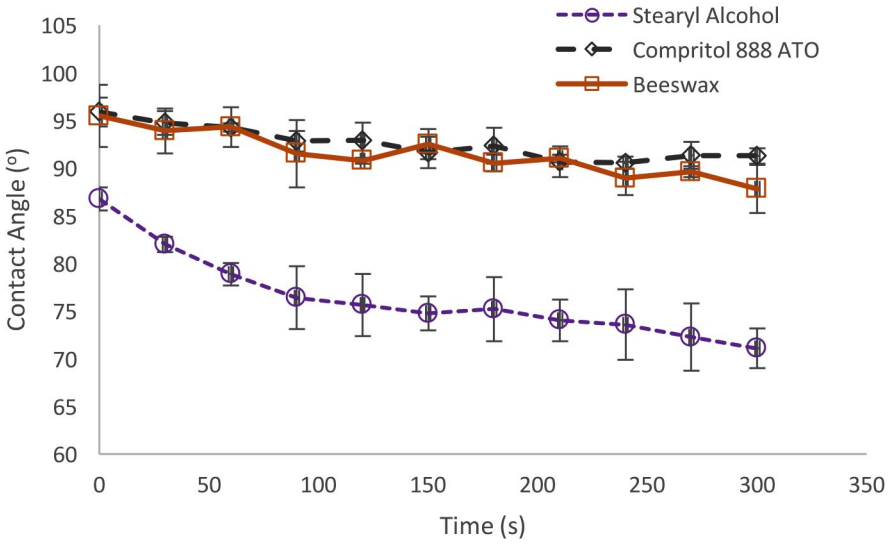

Figure 2. *Dynamic contact angle measurements of water on the surface of stearyl alcohol, Compritol 888 ATO, and beeswax.*

NMR diffusometry provides a measurement of the average volume to surface area ratio for permeated water within the pores, voids, and defects of these lipid matrices. This value is hereafter interpreted as a diffusion path length, $\bar{r}$, and is related to pore size.[6] Figure 3A shows a conceptual model of this experiment using 5 mm diameter monolithic samples prepared under similar slowly congealed conditions as the pellets used for dissolution studies above. During water permeation into the sample, $\bar{r}$ is expected to decrease as progressively finer pore structures are accessed, first showing long diffusion lengths associated with water present in the interface between the sample and NMR tube and then showing a shorter diffusion length as water begins to permeate radially inward into the lipid matrix. This methodology assesses the kinetics with which porous structures are permeated as well as their relative pore size.

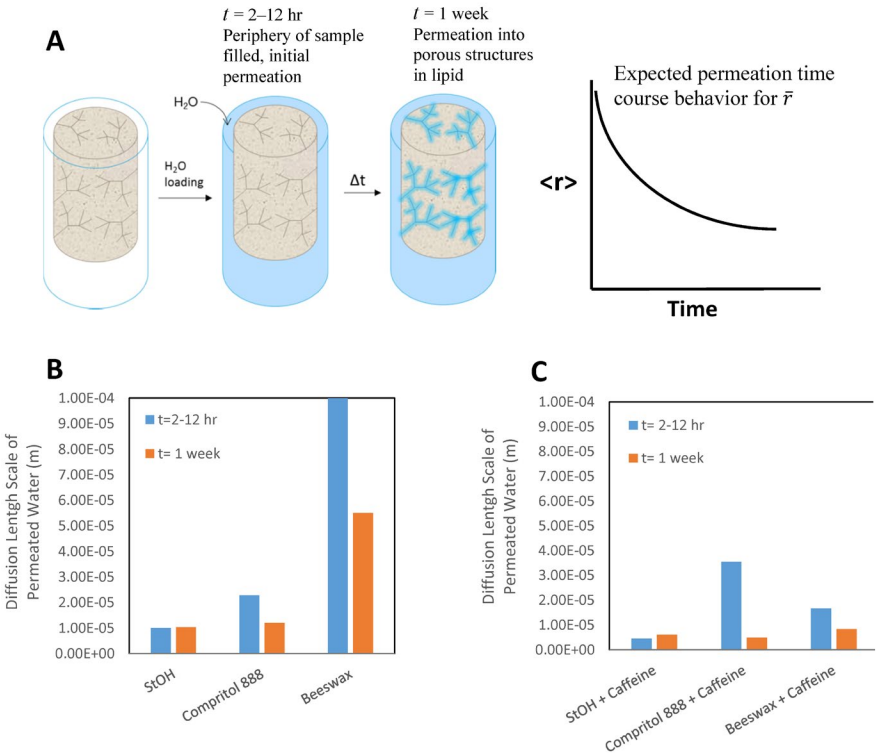

Figure 3. *(A) Diagram of water permeation NMR experiment. (B and C) Diffusion length scales of permeated water at t = 2–12 h and t = 1 week equilibration time at 25°C for monolithic samples of stearyl alcohol, Compritol 888 ATO, and beeswax (B) as well as their 30% caffeine formulations (C).*

Figure 3B shows that water permeates into a fine pore structure ($\bar{r}$ ~ 10 μm) in stearyl alcohol quickly following the start of permeation (2–12 h) with no further changes occurring out to one week. In contrast, water permeating through Compritol 888 ATO started at larger $\bar{r}$ and took one week to reach a comparable value to stearyl alcohol ($\bar{r}$ ~ 11 μm). Beeswax, even after one week, continued to exhibit a large value of $\bar{r}$. This water is proposed to fill the periphery of the sample at the NMR tube interface. These examples demonstrate that initial trends in wetting kinetics on the surface of these matrices shown in Figure 2 persist during long-term permeation of water into the matrices and provide a direct measurement of the different pore size distributions accessed by water in each matrix over time.

continued

Figure 3B demonstrates that the presence of crystalline API is associated with water permeation into a finer pore structure than in the placebo matrices, with $\bar{r}$ reaching 6–8 μm at one week exposure to water for all matrices. Both Compritol 888 ATO and beeswax reach this final state of permeation more slowly than stearyl alcohol (as assessed by the decrease in $\bar{r}$ over time). The presence of crystalline API presumably contributes to the porous network through partial dissolution of the crystalline material or by increasing the lipid grain boundary area around the caffeine crystals. Consistent with this interpretation, the presence of API in these matrices also has a strong impact on the volume fraction of permeated water, which can also be estimated from NMR spectra compared with an external standard. The volume fraction of permeated water in placebo matrices was estimated at 0.2, 0.9, and 3.0% for stearyl alcohol, Compritol 888 ATO, and beeswax, respectively. The presence of API increases the volume fraction of permeated water to 4.2, 3.5, and 6.1% for the same matrices. Addressing the rank ordering of these porosity values will be treated in a separate body of work.

Based on the experimental data above, we propose a model in which release rates from the binary lipid/caffeine formulations are rank ordered by movement of the wetting front through these matrices, which may be a co–rate limiting step for release of API. The presence of caffeine increases the extent of water permeation owing to its partial dissolution but does not change the rank order of wetting times or permeation rates. The aim of future work will be to inform decision making for this platform technology during formulation selection and process development by using magnetic resonance techniques to develop quantitative inputs into combined wetting front and diffusional flux models.

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Acute Care Cover for Severely Injured Limbs

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Saving Severely Injured Limbs in Military Settings

Traumatic limb injuries often occur in chaotic battlefield environments in which a soldier may not be transported to definitive care centers for up to 72 h (Fig. 1). The Acute Care Cover for Severely Injured Limbs (ACCSIL) is intended to fill the gap of medical care during this time span, providing medics with sophisticated tools in a lightweight, easily deployable system able to stop bleeding, prevent infection, regulate oxygen, and ultimately preserve viable tissue until the soldier is transported to a hospital. The ACCSIL system comprises an integrated device offering several benefits to the soldier. The outer cover provides bacterial resistance to prevent infection. The next layer contains an oxygen-generating polymer hydrogel component that can be triggered to release oxygen at a steady rate over 72 h upon application to a wound bed. The final layer is a bioactive gauze that is infused with compounds that can reduce oxidative stress by free radical scavenging while providing further antimicrobial functionality.

Role of Oxygen in Saving a Limb

Oxygen regulation is one of the key functions of this dressing. Especially when a tourniquet is used and the tissue beneath the tourniquet is wrapped in gauze and other protective material, lack of oxygen (hypoxia) can lead to tissue death.[1,2] On the other hand, the presence of reactive oxygen species (ROS) can also lead to tissue death through oxidative stress.[3] For ACCSIL, scientists have developed a polymer hydrogel that can store latent oxygen in a compact, lightweight polymer and deliver it to a wound bed on demand. At the same time, they have developed a complementary bioactive gauze capable of scavenging ROS. There are natural antioxidant enzymes the body uses to scavenge ROS; Battelle's device uses a much more stable and robust inorganic antioxidant to functionalize the surface of the gauze. This functionalized gauze has shown initial promise in mitigating cytotoxicity, especially under hypoxic conditions. The goal of this work is to investigate and demonstrate a proof of concept for a novel inorganic antioxidant functionalized gauze for reducing the oxidative stress in severe wounds, and ultimately, preserving tissue.

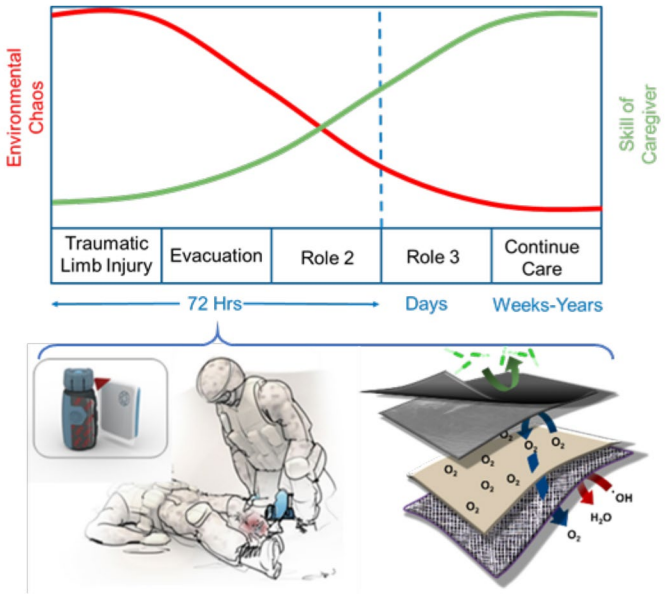

Figure 1. *The graph illustrates the inverse relationship between the environmental chaos and the sophistication of treatment over the ensuing time course after a serious limb injury. This results in the need for a lightweight, easily deployable wound dressing that can preserve a severely injured limb in the first 72 h. The dressing can be used with a tourniquet and serves to stop bleeding, prevent infection, provide oxygen, and scavenge radical oxygen species.*

Materials Tests Articles and Analysis Methods

Images of the test materials are shown in Figure 2. Several polymer blends were tested to tune the release profile of the oxygen-producing hydrogel. This polymer may be embedded within the wound dressing or used to power an external pump to deliver oxygen through the dressing to the wound bed. The bioactive gauze is functionalized with an inorganic antioxidant material and is applied directly to the wound bed and serves to help stop bleeding like a typical gauze. However, the gauze is also imbued with the ability to scavenge radical species that lead to further tissue death, thus preserving viable tissue while the soldier is transported to a hospital.

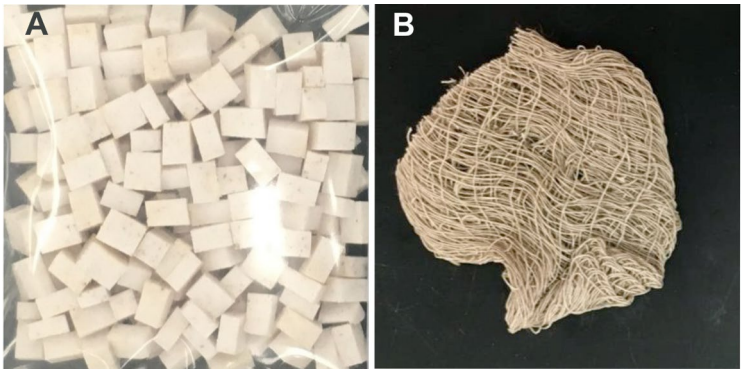

Figure 2. *(A) Oxygen-producing polymer containing latent oxygen entrapped in a polymer matrix designed to release gaseous oxygen in a sustained manner over 72 h in response to water uptake from the wound exudate. (B) Bioactive gauze designed to be applied directly to the wound bed and scavenge for radical reactive oxygen species.*

The release profiles from the oxygen-generating hydrogel were characterized using an oxygen displacement method. Briefly, oxygen release was activated by hydrating the polymer in a beaker. The oxygen generated was directed through tubing

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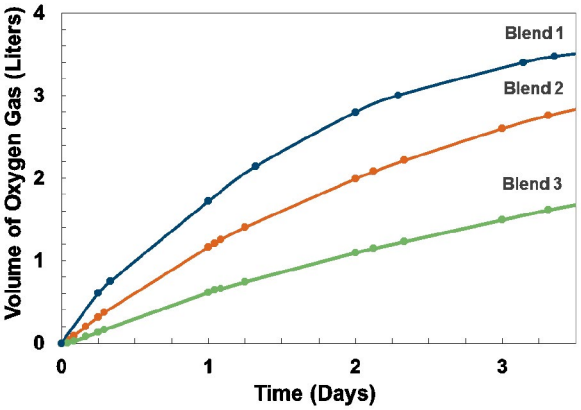

Figure 3. *Oxygen release profiles measured via oxygen displacement for three polymer hydrogel blends.*

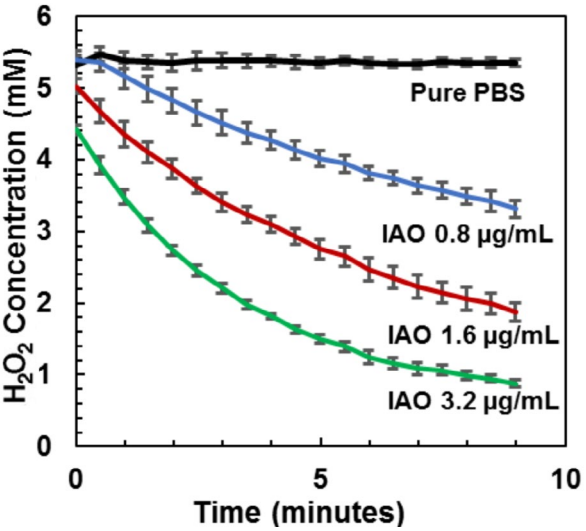

Figure 4. *Kinetic hydrogen peroxide decomposition curves for various aqueous dilutions of inorganic antioxidant (IAO) mixed with 5 mM hydrogen peroxide. UV absorbance measurements at 240 nm were recorded in triplicate in a UV transparent 96-well plate every 30 s for 9 min.*

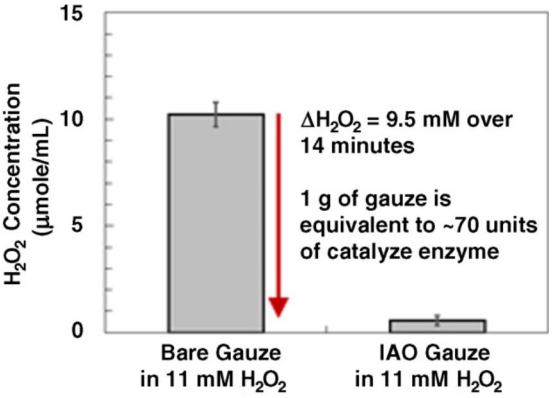

Figure 5. *The endpoint hydrogen peroxide decomposition data for triplicate 100 mg samples of functionalized gauze immersed in 10 mL of 11 mM H_2O_2.*

into a graduated cylinder filled with water and fixed inverted in a larger beaker of water. The oxygen generated displaced the water and was measured by the cylinder graduations. Hydrogen peroxide decomposition was tracked as a measure of reactive oxygen scavenging capacity of the gauze. Several dilutions of the inorganic antioxidant were dispersed in hydrogen peroxide (5 µmol/mL). As the inorganic antioxidant decomposed the hydrogen peroxide, the decrease in concentration was tracked by measuring UV absorbance at 240 nm. Likewise, the hydrogen peroxide decomposition capacity of the gauze was measured by immersing the approximately 100 mg pieces of gauze in 10 mL of 11 mM H_2O_2. The endpoint amount of H_2O_2 decomposition was determined by measuring the amount of H_2O_2 remaining after 10 min via absorbance at 240 nm.

Sustained Release of Oxygen Over 3 Days

The release profiles for three oxygen-producing polymer hydrogel blends show a near linear, tunable sustained release over 3 days (Fig. 3). By tuning the relative hydrophilicity of the polymer blend, various release profiles are achievable. Moreover, the material has a very high oxygen-producing capacity in a low-weight package. The polymer can produce over 3 L of gaseous oxygen over 3 days for every 100 g of active compound. These polymer hydrogels are currently being integrated into a conformal cover to yield an oxygen chamber that can deliver oxygen to otherwise hypoxic wounded tissue.

In Vitro Activity of the Inorganic Antioxidant Gauze

Hydrogen peroxide is an example of one ROS involved in oxidative stress in wounds. The active inorganic antioxidant showed dramatic ability to decompose hydrogen peroxide *in vitro* (Fig. 4). Doses as low as 3.2 µg/mL of the antioxidant could decompose 5 µmol/mL concentrations of hydrogen peroxide in about 10 min. Next, the same test was conducted on the functionalized gauze to see if the antioxidant maintained efficacy on the gauze. Figure 5 shows that a 100 mg piece of functionalized gauze decomposed 9.5 µmol/mL of the hydrogen peroxide in a 10 mL volume of 11 mM hydrogen peroxide within 14 min. This correlates roughly with the hydrogen peroxide decomposing capacity of about 70 units of catalase enzyme per gram of functionalized gauze. The unfunctionalized control gauze showed no change in hydrogen peroxide concentration.

Conclusions and Future

This work demonstrates how controlled release technology is being integrated into a lightweight, portable device that allow medics to supply oxygen to a wound and scavenge ROS while protecting the wound from the environment. Battelle will continue to integrate this technology with other bioactives to aid with fighting infection, preserving tissue, and arresting bleeding.

Acknowledgement

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Announcement: 16th International Conference on "Advances in Technology and Business Potential of New Drug Delivery Systems"

Anisha Pargal, President, CRS India Local Chapter

The CRS India Local Chapter announces a call for abstracts for the 16th international conference on "Advances in Technology and Business Potential of New Drug Delivery Systems," which will take place February 23–24, 2018, in Mumbai, India. The venue is Hotel Lalit, Sahar Airport Road, Andheri (East) Mumbai.

In the quest to deliver therapeutic agents with improved efficacy and minimum side effects, novel drug delivery systems (NDDS) have created a paradigm shift in the pharmaceutical market. The thrust behind development of NDDS has increased owing to its manifold advantages such as safety, high efficacy, improved pharmacokinetics, decreased dosing frequency, minimization of side effects on account of targeting capability to a specific site, patient compliance, and economic advantages. The burgeoning interest in NDDS has increased due to advancement and availability of a variety of technologies to deliver drugs in novel dosage forms. The novel drug delivery systems include various nanocarrier-based drug delivery systems such as liposomes, niosomes, micelles, nanoparticles, and so on and administration technologies resulting in site-specific delivery. These delivery systems make it possible to administer drugs through routes that were not explored earlier, such as microneedles for transdermal drug and vaccine delivery, depot systems for intramuscular administration, aerosolized systems for pulmonary delivery, and so on. It is estimated that NDDS products contribute to 17% of the world's pharma market, amounting to $104 billion.

In view of this, the 16th symposium of CRS India Local Chapter aims to explore the upcoming developments in the field of NDDS and provide a common platform to industry personnel, academicians, research scientists, and students to stimulate discussions on various aspects of development and management of novel delivery systems including regulatory issues and business aspects. Poster sessions will provide opportunities for researchers to showcase their novelty in various aspects of drug delivery and will serve as an interactive forum between delegates from academia and industry.

Nine invited international speakers have confirmed their participation: Per Falk (Ferring Pharmaceuticals, Switzerland), Henning Falck (Neuhaus Neotec, Germany), Michelle Frisch (Powder Systems Ltd., U.S.A.) , Hamid Ghandehari (University of Utah, U.S.A.), Vinod Labhasetwar (Cleveland Clinic, U.S.A.), Dilwyn Patterson (GEA Process Engineering, United Kingdom), Kannan Rangaramanujan (John Hopkins School of Medicine, U.S.A.), Sudesh Shetty (KPMG, India), and Matthias Wacker (Goethe University, Germany). International coordinators are Vinod Labhasetwar, Ryan Donnelly (Queen's University, Belfast, Ireland), and Paul Heng (National University of Singapore).

Students, academicians, and researchers are invited to present their research related to the theme of the seminar at the poster presentation competition. The deadline for abstract submission is December 10, 2017, and the registration deadline is January 31, 2018. For further information, please contact secretary.crsic@gmail.com or president.crsic@gmail.com. Please also visit www.crsic.org. ■

CRS Nordic Chapter Meeting

Bente Steffansen,[1] Marika Ruponen,[2] Jarkko Rautio,[2] and Ingunn Tho[3]

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

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

The first part of the scientific program was devoted to transport across the blood-brain barrier (BBB) and chaired by Marika Ruponen. Invited speaker Tetsuya Terasaki (Tohoku University, Japan) opened this part with the lecture "Retro-enantio Peptide of Transferrin Receptor Binding Peptide (D-THRre) as a Blood-Brain Barrier Permeable Stable Carrier." He talked about how the retro-enantio peptides with their increased circulation time as compared with the parent peptide show promising results for brain delivery via receptor-mediated transcytosis utilizing the highly BBB-expressed transferrin receptor. The next speaker was Kati-Sisko Vellonen (University of Eastern Finland) with the presentation "Effect of Alzheimer's Disease (AD) on Drug Transporters in Brain." She introduced her study about profiling transporters and tight junction markers in AD mice models showing only minor disease-induced alterations in all studied AD animal models. The last speaker before the coffee break was Jarkko Rautio (University of Eastern Finland) with the presentation "LAT-1 Transporter as Pathway Across Blood-Brain Barrier." He presented their research on prodrugs, such as ketoprofen-tyrosine, that are substrates for the L-type amino acid transporter (LAT-1) highly expressed on BBB. The last segment before lunch was dedicated to the short poster presentations from young researchers, and 13 enthusiastic and engaging presentations were delivered.
The afternoon session was devoted to clinically relevant drug transporters and chaired by Jarkko Rautio. Invited speaker Peter Swaan (University of Maryland, U.S.A.) opened
this session with his lecture "Modeling and Simulation of Drug Transport: Challenges
and Successes." He talked
about identifying a new class
for p-glycoprotein (Pgp) drug interaction with a neural network type model by
studying Pgp-drug interactions of 1,500 drugs in DrugBank. The next invited speaker was Heidi Kidron (University of Helsinki), whose lecture was "Single Nucleotide Polymorphisms (SNPs) Located in the Transmembrane Regions of Breast Cancer Resistant Protein (BCRP) Impair the Expression and Transport Activity." She lectured about performing a number of naturally occurring BCRP variants in vesicles from sf9 insect cells or human embryonic kidney (HEK) 293 cells. She showed that the efflux of BCRP probe substrates estrone-3-sulphate (E3S) and Lucifer yellow were reduced in the cells expressing variants compared with wild type (WT)

continued

[1] University of Southern Denmark.
[2] University of Eastern Finland.
[3] University of Oslo, Norway.

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

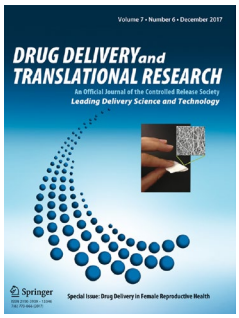
BCRP and, thereby, that transmembrane regions of BCRP were sensitive to amino acid substitution. Thus, patients with these BCRP variants could suffer from unexpected pharmacokinetic events of substrate drugs. The last lecture was presented by Mikko Niemi (University of Helsinki) who talked about "Pharmacogenomics of Drug Transporters." He showed that patients expressing the SNP of organic anion transporter (OATP)1B1–521CC could have significantly increased pravastatin plasma concentrations compared with patients with WT OATP1B1.

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

Drug Delivery and Translational Research Update

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

2017 *DDTR* Parameters



DDTR, an official journal of CRS, continues to improve the quality of published papers that are particularly focused on translational aspects of drug delivery science and technology. The journal also encourages submissions that are innovative and address critical drug delivery related issues or if the study is mechanistic. We also encourage reporting of negative data from a well-designed study with a rationale but that did not produce the expected outcome. Authors for such articles are expected to provide possible reasons for failure and what could be an alternative rationale. Reviews should be on current topics of interest in drug delivery and must include critical analysis of the information and not just a compilation of literature (see the author's instructions). *DDTR*'s acceptance rate as of October 31, 2017, based on the articles submitted and accepted during 2017, is approximately 27%, and an average time to final decision for accepted manuscripts is approximately 3 months. The decision time on manuscripts that are rejected, including the articles rejected without review, is approximately 3 weeks.

***DDTR* Special Issue: Drug Delivery in Female Reproductive Health**

This special theme issue has its origin in a previous theme issue on advances in vaginal drug delivery published in *DDTR* in June 2011. That issue was based on a scientific session held at the CRS Annual Meeting in Portland, Oregon, in July 2010. The goal for the current issue is to provide a more expansive look at drug delivery as it relates to female reproductive health. As such, it provides reviews on long-acting systemic HIV pre-exposure prophylaxis. These long-acting systems fall into one of two general categories: injectable and implantable. Despite challenges observed with peri-coital administration of vaginal gels, work continues on development of on-demand products for prevention of HIV and other sexually transmitted infections (STIs). The use of electrospun fibers is covered: prevention of acquisition of STIs including HIV, contraception, other reproductive tract infections, and use in the field of multipurpose prevention technologies (MPTs). There are several vaginal dosage forms being investigated for treatment and reduction of recurrence of cervical cancer including inserts (tablets), rings, bioadhesive dosage forms, and cervical caps. Two other female reproductive conditions affecting many women worldwide are endometriosis and uterine fibroids. The use of drug delivery to address these two conditions is reviewed. Finally, a research article describes research on an MPT product that can potentially release three antiviral agents and a contraceptive. Access this special issue (vol. 7, no. 6, pp. 773–866) at https://link.springer.com/journal/13346/7/6/page/1.

About the Guest Editor

David R. Friend is the chief scientific officer at Evofem Biosciences in San Diego, California. The company is developing contraceptive and STI prevention products. Prior to joining Evofem, he was director of product development and associate professor of obstetrics and gynecology at CONRAD, a division of the OB-GYN department of Eastern Virginia Medical School. Prior to his time at CONRAD, he worked for several small to midsize pharmaceutical companies. He started his career at SRI International working with Jorge Heller. He serves on a number of scientific advisory boards as well as editorial boards, including *DDTR*.

Special Issues

DDTR has thus far published 18 special issues covering different aspects of drug delivery in different disease conditions. Four 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 labhasv@ccf.org for consideration.

***DDTR* Outstanding Paper Award**

Join the leading scientists who are publishing their work in *DDTR* and also compete for the 2018 *DDTR* outstanding research/clinical paper award. The paper will be selected from the research articles/clinical research/clinical trials published in *DDTR* during 2018. The award will be presented at the 46th CRS annual meeting. Visit the CRS website (www.controlledreleasesociety.org/about/Awards/Pages/DDTROustandingPaper.aspx) for the award criteria. ■

People in the News

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

biOasis Announces Formation of Scientific Advisory Board to Advance the Science for the Company's Blood-Brain Barrier Drug Delivery Platform

Business News: September 7, 2017 – VANCOUVER, BC, Canada – biOasis Technologies Inc. (OTCQB: BIOAF; TSX.V: BTI), a biopharmaceutical company focused on overcoming the limitations of therapeutic drug delivery across the blood-brain barrier (BBB) and into the central nervous system for the treatment of neurological diseases and disorders, today announced the appointments of Prof. John H. Krystal, M.D., Jeffrey L. Cummings, M.D., and John P. Wikswo, Jr., Ph.D., to its newly established Scientific Advisory Board (SAB). These independent experts will serve as a strategic resource to biOasis as it continues to advance the company's proprietary drug delivery platform. Dr. Krystal will serve as chairman of the SAB.

"I'm excited to serve as chair of the biOasis SAB and to work with Mark again," said Dr. Krystal. "Most drugs created to treat central nervous system diseases and disorders fail because they aren't optimally designed to be delivered in sufficient quantities to the brain. I look forward to working with Mark and his team to untap the potential of the biOasis platform in the development of differentiated treatments for previously untreatable neurological diseases and disorders."

Additional members will be added once their institutions approve their membership to the biOasis SAB. The SAB will be composed of leaders from the academic, pharmaceutical, and biotechnology industries from discovery, translational medicine, and clinical development areas. The SAB will work closely with the biOasis management team to advance the development of the company's proprietary BBB drug delivery platform, xB3. The role of the SAB is to provide strategic guidance and direction for the biOasis in-house development programs as well as strategic research alliances. The SAB will also play a role in guiding and prioritizing the company's research investment.

"I am intrigued by the proprietary xB3 BBB drug delivery technology that biOasis has developed, and I am eager to assist with the strategy for its development," said Dr. Cummings.

"I am excited at the opportunity of working with biOasis and their SAB. This is translational science at its best—my academic research group received five years of funding from NIH/NCATS to develop a neurovascular unit on a chip and the supporting hardware. We learned a lot from our experiments, colleagues, pharma, and organ-on-chip companies, and are proceeding to develop on-chip disease models. Now I can help guide the development of a specific therapeutic platform," said Dr. Wikswo.

"We are honored to welcome Dr. Krystal, Dr. Cummings, and Dr. Wikswo to the new biOasis SAB. Having worked with Profs. Krystal and Cummings previously, I've been fortunate to have had their guidance and support on several key studies. They helped guide my translational research during one of the most productive periods in my career. I can't wait to work with them again. Dr. Wikswo adds significant BBB experience to our board. His work developing a BBB on a chip as part of his organs-on-a-chip program has been extraordinary, and I look forward to working with him as well. They are all true leaders in their fields," said Mark Day, Ph.D., president and chief executive officer, biOasis Technologies, Inc. "Our new SAB members will provide a tremendous knowledge base that will help to inform our approach to our ongoing research and clinical development activities. Their collective knowledge and guidance will be invaluable as we advance our in-house research programs and external research alliances."

Prof. John H. Krystal, M.D., is the Robert L. McNeil, Jr., professor of translational research, chair of the department of psychiatry, and professor of neuroscience at the Yale University School of Medicine and chief of psychiatry at Yale–New Haven Hospital. Dr. Krystal has published extensively on the neurobiology and treatment of schizophrenia, alcoholism, post-traumatic stress disorder (PTSD), and depression. Notably, he led the discovery of the rapid antidepressant effects of ketamine in humans. Dr. Krystal is the director of the National Alcohol Abuse and Alcoholism Advisory Council Center for the Translational Neuroscience of Alcoholism and the Clinical Neuroscience Division of the VA National Center for PTSD. Dr. Krystal is a member of the U.S. National Academy of Medicine. Currently, he is president of the International College of Neuropsychopharmacology, a member of the National Institute of Mental Health National Mental Health Advisory Council, and editor of *Biological Psychiatry*.

Dr. Krystal received his bachelor of science degree in behavioral sciences from the University of Chicago and his doctor of medicine degree from Yale University School of Medicine. He completed his residency in the Yale Psychiatry Residency Training Program.

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Jeffrey L. Cummings, M.D., is director of the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas and Cleveland, the Camille and Larry Ruvo Chair of the Neurological Institute of Cleveland Clinic, and professor of medicine (neurology) at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. Dr. Cummings is principal investigator/director of the National Institutes of Health/National Institute of General Medical Sciences-funded Center for Neurodegeneration and Translational Neuroscience.

Dr. Cummings is a world-renowned Alzheimer's researcher and leader of clinical trials. He has been recognized for his research and leadership contributions in the field of Alzheimer's disease through the Henderson Award of the American Geriatrics Society (2006), the Ronald and Nancy Reagan Research Award of the national Alzheimer's Association (2008), and the Lifetime Achievement Award of the Society for Behavioral and Cognitive Neurology (2017). In 2010, he was honored by the American Association of Geriatric Psychiatry with their Distinguished Scientist Award. He was featured in the *Gentleman's Quarterly* (June 2009) as a "Rockstar of Science." Dr. Cummings' interests embrace clinical trials, developing new therapies for brain diseases, and the interface of neuroscience and society.

Dr. Cummings was formerly a professor of neurology and psychiatry at the University of California, Los Angeles (UCLA), director of the Mary S. Easton Center for Alzheimer's Disease Research at UCLA, and director of the Deane F. Johnson Center for Neurotherapeutics at UCLA. He is past president of the Behavioral Neurology Society and of the American Neuropsychiatric Association. Dr. Cummings has authored or edited 39 books and published over 700 peer-reviewed papers.

Dr. Cummings completed his neurology residency and a fellowship in behavioral neurology at Boston University, Boston. His U.S. training was followed by a research fellowship in neuropathology and neuropsychiatry at the National Hospital for Nervous Diseases, Queen Square, London.

John P. Wikswo, Jr., Ph.D., is the Gordon A. Cain University Professor at Vanderbilt University and is the founding director of the Vanderbilt Institute for Integrative Biosystems Research and Education. He has been on the Vanderbilt faculty since 1977. His research has included superconducting magnetometry, the measurement and modeling of cardiac, neural, and gastric electric and magnetic fields and nondestructive testing of aging aircraft. In 1980, he and his group made the first measurement of the magnetic field of a nerve impulse.

As a tenured member of the departments of biomedical engineering, molecular physiology and biophysics, and physics and astronomy, he is guiding the development of microfabricated devices, optical instruments, and software for studying how living cells interact with each other and their environment and respond to drugs, chemical/biological agents, and other toxins, thereby providing insights into systems biology, physiology, medicine, and toxicology.

He has over 200 publications, is a fellow of seven professional societies, and has received 22 patents. He loves teaching and learning, and sharing his enthusiasm for research and inventing with high-school students, undergraduates, and graduate students. He is happiest when he is tinkering and doing plumbing, carpentry, and wiring, either on his house or the ones that he and his group are building to grow cells and miniature human organs. His group's work on organ-on-chips focuses on the development of intelligent well plates that serve as perfusion controllers, microclinical analyzers, and microformulators; developing a blood-brain barrier on a chip; and integrating multiple organs to create a milli-homunculus from coupled organs on chips. To learn more about the development of a microfluidic device containing human cells, which can model the blood-brain barrier, visit www.technologynetworks.com/neuroscience/videos/blood-brain-barrier-on-a-chip-290733.

Dr. Wikswo trained as a physicist, and he received his bachelor of arts degree from the University of Virginia and his doctor of philosophy degree from Stanford University.

biOasis Technologies Inc. is a biopharmaceutical company focused on overcoming the limitations of therapeutic drug delivery across the blood-brain barrier (BBB). The delivery of therapeutics across the BBB represents the single greatest challenge in treating neurological disorders. The company is developing and commercializing a proprietary brain delivery technology to address unmet medical needs in the treatment of central nervous system diseases and disorders. The company maintains headquarters in Vancouver, Canada, with offices in Connecticut, United States. biOasis trades on the OTCQB under the symbol "BIOAF" and on the TSX Venture Exchange under the symbol "BTI." For more information about the company, please visit www.bioasis.ca.

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BioDelivery Sciences President and Chief Executive Officer Dr. Mark A. Sirgo to Retire at Year-End While Continuing as Vice Chairman

PRNewswire: August 23, 2017 – RALEIGH, NC, U.S.A. – BioDelivery Sciences International, Inc. (NASDAQ: BDSI) announced today that at the end of 2017, Dr. Mark A. Sirgo will retire as BDSI's president and chief executive officer, roles which he has held since 2005. Dr. Sirgo will remain as vice chairman of the Board of Directors, where he will continue to provide leadership and guidance to BDSI. Dr. Sirgo and the Board will work together during the coming months to determine his successor.

"After 13 years of leading BDSI from a start-up through three drug approvals and the creation of a fully integrated pharmaceutical company, highlighted by the recent reacquisition and early commercial success of BELBUCA®, the business is very well positioned for long-term growth. With the outstanding team we have built and the overall strength of the business, year-end felt like the appropriate time for me to retire from my day-to-day role," said Dr. Sirgo. "Announcing my plans now allows for the timely selection and onboarding of my replacement, a proven leader with significant commercial experience, before year-end. In my ongoing role as vice chairman, I will continue to offer my guidance to ensure a smooth and thoughtful management transition while also providing strategic insight for the growth of BDSI, as we continue to focus and execute on our commercial strategy. In addition, during the next several months, I will be working with our experienced management team to achieve the goals I publicly outlined earlier this year, the most important of which are hitting our revenue target and continuing to evaluate strategic opportunities to enhance shareholder value."

Dr. Sirgo was one of two founders of Arius Pharmaceuticals, which was merged with BDSI in August of 2004. Arius brought to BDSI the BioErodible MucoAdhesive film (BEMA®) technology that became the platform from which BDSI's product pipeline evolved. Dr. Sirgo successfully led the company through the clinical development, U.S. Food and Drug Administration (FDA) approvals, and launches of ONSOLIS® (fentanyl buccal soluble film), BUNAVAIL® (buprenorphine and naloxone) buccal film, and BELBUCA® (buprenorphine) buccal film, while simultaneously transforming BDSI into a fully integrated pharmaceutical company. Early commercialization partnerships with companies including Meda Pharmaceuticals, and later with Endo Pharmaceuticals and Collegium Pharmaceutical, secured nearly $250 million in partnering dollars, allowing BDSI the opportunity to develop its pipeline while limiting the use of the company's equity. More recently, Dr. Sirgo was instrumental in the reacquisition of BELBUCA® under favorable financial terms from Endo, which has strengthened the commercial future of BDSI.

"Mark's accomplishments during his tenure reflect his commitment to hard work, a continual focus on building a quality pharmaceutical company, and unwavering dedication to creating shareholder value," stated Dr. Frank O'Donnell, chairman of BDSI's Board. "Mark's leadership and vision for drug development, much of which has been built from the BEMA platform that was acquired when Mark joined BDSI, have been instrumental to BDSI's growth, including three successful drug approvals and the launch of a full commercial organization. We thank Mark for his innumerable contributions to BDSI and look forward to Mark's continued leadership through this transition and his continued guidance as vice chairman."

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

BDSI's marketed products and those in development address serious and debilitating conditions such as breakthrough cancer pain, chronic pain, and opioid dependence. BDSI's headquarters is in Raleigh, North Carolina.

Marvin J. Slepian, M.D., to Be Honored with the AZBio Pioneer Award for Lifetime Achievement at the 2017 AZBio Awards

Business Wire: August 8, 2017 – CHANDLER, AZ, U.S.A. – The Arizona Bioindustry Association will honor Marvin J. Slepian, M.D., of the University of Arizona with the AZBio Pioneer Award for Lifetime Achievement at the 2017 AZBio Awards. Arizona life science and business leaders, as well as guests from across the country, will be on hand to applaud Dr. Slepian for a body of work that has made life better for people at home and around the world.

The maxim, "If you need to get something done, ask a busy person," often has been attributed to Benjamin Franklin. Dr. Slepian is someone Franklin would have recognized as a kindred spirit.

Dr. Slepian is a cardiologist, inventor, entrepreneur, educator, innovator, and more. At the UA, he serves as professor of medicine, professor and associate department head of biomedical engineering, professor of material sciences and engineering, professor of medical imaging, McGuire Scholar in the UA Eller College of Management, and member of the UA Sarver Heart Center. Dr. Slepian also is the founder and director of the newly created Arizona Center for Accelerated Biomedical Innovation (ACABI)—a "creativity engine" focused on novel solution development for unmet medical needs.

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Dr. Slepian attended Princeton (A.B. biochemical sciences and science in human affairs 1977) and received his medical degree from the University of Cincinnati College of Medicine (1981 AOA). He completed his residency in internal medicine at New York University–Bellevue Hospital in New York, where he served as chief resident in medicine; his clinical and research fellowships in cardiology at Johns Hopkins University School of Medicine in Baltimore; and his clinical and research fellowships in interventional cardiology and a research fellowship in artificial organs at the Cleveland Clinic in Cleveland, Ohio. In addition, Dr. Slepian received postdoctoral training in chemical engineering and polymer chemistry at Washington University and MIT.

With a career that spans the spectrum from basic and translational research to technology transfer, Dr. Slepian exemplifies how keen clinical observation coupled with solid basic science knowledge and exploration in the lab can successfully transition to commercial products that make life better for patients. At the basic level, his laboratory has focused on three main areas: 1) the role of cell-matrix interactions in vascular disease, 2) the role of physical forces in modulating vascular cell and platelet behavior, and 3) the utility of polymeric biomaterials to modulate cell-matrix interactions, as well as serve as novel therapeutic structural, barrier, or drug-delivery materials. On the translational level, his lab has developed many novel therapeutic solutions based on polymeric biomaterials that have found their way into clinical use today, including drug-eluting stent technologies, stent coatings, "polymer paving," surgical anti-adhesive barriers, synthetic tissue and vascular sealants, myocardial revascularization and cell-delivery methods, and cardiovascular prosthetic devices, including the total artificial heart.

Dr. Slepian has founded or cofounded several medical device companies, including Focal (which went public in 1997 and was acquired by Genzyme Biosurgery in 2001), EndoTex Interventional Systems Inc. (acquired by Boston Scientific in 2007), Angiotrax, Hansen Medical (which went public in 2006 and was acquired by Auris Surgical Robotics in 2016), Arsenal Medical and its spinout company 480 BioMedical, and MC10, which takes rigid high-performance electronics and reshapes them into human-compatible form factors that stretch, bend, and twist to move with the body. He has been involved with bringing many new devices through the FDA regulatory process into clinical use, including most notably the total artificial heart. Dr. Slepian was the founding president of SynCardia Systems, Inc., and served in multiple roles, including chief scientific officer, president, and chairman for more than a decade. Today, the SynCardia total artificial heart is the only artificial heart commercially available in the United States, European Union, and Canada for use as a bridge to donor heart transplantation.

Dr. Slepian has received multiple awards for his academic and translational research and innovation activities, including election as a Fellow of the American Institute for Medical and Biological Engineering (AIMBE) and the National Academy of Inventors (NAI), and has been a frequent visiting professor and lecturer in medicine (cardiology), biomedical engineering, and innovation, both nationally and internationally. He is the author of numerous publications; holds patents in the fields of vascular biology, thrombosis, polymeric biomaterials, local drug delivery, medical device development, and artificial organs; is an active reviewer for multiple journals; and is a consultant for academia, industry, and governmental agencies. Most recently, Dr. Slepian has served as president of the International Society for Mechanical Circulatory Support (ISMCS), secretary/treasurer of the American Society for Artificial Internal Organs (ASAIO), and as annual meeting program chair of both of these societies for 2017.

For a lifetime of leadership, vision, and commitment to making life better in Arizona and around the world, Marvin J. Slepian, M.D., is being honored with the 2017 Arizona Bioscience Pioneer Award for Lifetime Achievement. A ceremony honoring Dr. Slepian will take place at the AZBio Awards on October 11 at the Phoenix Convention Center.

The AZBio Awards ceremony celebrates Arizona's leading educators, innovators, and companies. Each year, AZBio honors bioindustry leaders from across the state of Arizona who are illustrative of the depth, breadth, and expertise of its bioscience industry. The AZBio Awards ceremony is held annually during Arizona Bioscience Week. AZBW 2017 was proclaimed by the Arizona Senate earlier this year. Multiple educational events focused on the value of life science innovation will take place from October 8 to 14, including the BMES Annual Meeting in Phoenix. The Biomedical Engineering Society (BMES) is the world's leading society of professionals devoted to developing and using engineering and technology to advance human health and well-being. Attendees at BMES 2017 in Phoenix are expected to include nearly 4,000 professional scientists, engineers, researchers, and students from academia and industry who are leaders in biomedical engineering. For registration and more information, go to www.azbioawards.com. For more information on Arizona Bioscience Week, visit www.AZBio.org/AzBW.

A key component in Arizona's life science ecosystem, the Arizona Bioindustry Association (AZBio) is the only statewide organization exclusively focused on Arizona's bioscience industry. AZBio membership includes patient advocacy organizations, life science innovators, educators, healthcare partners, and leading business organizations. AZBio is the statewide affiliate of the Biotechnology Innovation Organization (BIO) and works in partnership with AdvaMed, MDMA, and PhRMA to advance innovation and to ensure that the value delivered from life-changing and life-saving innovation benefits people in Arizona and around the world. For more information, visit www.AZBio.org and www.AZBio.TV. ■

Companies in the News

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

September

TherapeuticsMD Announces Submission of Additional Endometrial Safety Information to the New Drug Application for TX-004HR

Business Wire: September 14, 2017 – BOCA RATON, FL, U.S.A. – TherapeuticsMD, Inc. (NYSE American: TXMD), an innovative women's healthcare company, today announced the submission of the additional endometrial safety information that was requested by the Food and Drug Administration (FDA) in its recent General Advice Letter to the company to the New Drug Application (NDA) for TX-004HR. The company has scheduled a formal meeting with the FDA for November 3, 2017, at which the company expects to learn if this additional endometrial safety data addresses the lack of long-term safety identified in the Complete Response Letter for the NDA for TX-004HR. The company currently plans to resubmit the NDA for TX-004HR shortly after the meeting.

The submission includes a comprehensive, systematic review of the medical literature on the use of vaginal estrogen products and the risk of endometrial hyperplasia or cancer, including the safety data from the recently published Women's Health Initiative Observational Study of vaginal estrogen use in postmenopausal women and information on the relevance of the first uterine pass effect for low-dose vaginal estrogen products.

"Our comprehensive, systematic review of the medical literature on the use of vaginal estrogen products is compelling, and the totality of the data demonstrates that these products are not associated with increased risks of endometrial hyperplasia or cancer," said TherapeuticsMD chief clinical officer Brian Bernick. "We believe this is an important step towards the approval of our NDA for TX-004HR, and we look forward to meeting with the FDA in November to discuss our path forward."

TherapeuticsMD, Inc., is an innovative healthcare company focused on developing and commercializing products exclusively for women. With its SYMBODA™ technology, TherapeuticsMD is developing advanced hormone therapy pharmaceutical products to enable delivery of bio-identical hormones through a variety of dosage forms and administration routes. The company's late-stage clinical pipeline includes two phase 3 product candidates: TX-001HR for treatment of moderate-to-severe vasomotor symptoms (VMS) due to menopause and TX-004HR for treatment of moderate-to-severe vaginal pain during sexual intercourse (dyspareunia), a symptom of vulvar and vaginal atrophy (VVA) due to menopause. The company also manufactures and distributes branded and generic prescription prenatal vitamins under the vitaMedMD® and BocaGreenMD® brands.

Seqirus Receives FDA Approval of Afluria Quadrivalent® (Influenza Vaccine) for People Five Years of Age and Older in the United States

Business Wire: September 14, 2017 – CAMBRIDGE, MA, U.S.A. – Seqirus announced today that the U.S. Food and Drug Administration (FDA) has approved Afluria Quadrivalent (influenza vaccine) for use in people five years of age and older, extending the company's broad portfolio of influenza vaccine offerings. Afluria Quadrivalent, which was first approved in the United States in August 2016 for people aged 18 and older, helps protect against two influenza A strain viruses and two B strain viruses.

"Pediatric health care providers now have a new vaccine option to help protect children five years and older against influenza," said Gregg Sylvester, M.D., vice president of medical affairs at Seqirus. "As the only global vaccine company solely dedicated to influenza, we are committed to providing health care professionals and their patients with the broadest range of vaccine options available."

The traditional seasonal influenza vaccine is a trivalent formula consisting of two strains of influenza A virus and a single strain of influenza B virus. However, since 1985, two distinct lineages of influenza B virus have co-circulated with varying dominance. The use of a four-strain influenza vaccine like Afluria Quadrivalent may now provide protection against both B lineages.

The U.S. Centers for Disease Control and Prevention (CDC) recommends annual influenza vaccination for everyone six months of age and older. Recently, the CDC's Advisory Committee on Immunization Practices (ACIP) voted to include Afluria® (influenza vaccine) as one of the recommended trivalent influenza vaccine options for people aged five years and older for the upcoming 2017–2018 season. The CDC has accepted the ACIP recommendation in its 2017–2018 influenza recommendations published in the August 25, 2017, *Morbidity and Mortality Weekly Report*. As a result, both Afluria and Afluria Quadrivalent are now both licensed and recommended for people aged five years and older.

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Afluria Quadrivalent and Afluria are both available in the United States for the 2017–2018 influenza season as part of the extensive Seqirus influenza vaccine portfolio. Both are presented in prefilled syringes as well as multidose vials, and are the only influenza vaccines with a needle-free injection delivery option (PharmaJet® Stratis® 0.5 mL needle-free jet injector) for people aged 18–64 years.

As the only global vaccine company solely dedicated to the prevention of influenza, the complete Seqirus portfolio of seasonal influenza vaccines includes both trivalent and quadrivalent options, manufactured using egg- and cell-based technologies, to provide a wide range of options for people aged four years and older. The portfolio also includes the only adjuvanted seasonal influenza vaccine specifically developed for people 65 years and older.

In a randomized, double-blind, active-controlled clinical trial conducted in 3,395 subjects aged 18 years and older, Afluria Quadrivalent demonstrated noninferiority to two TIV comparators for all influenza strains contained in the vaccine. Additionally, noninferiority was demonstrated for both endpoints in both age subgroups, adults aged 18 through 64 years and 65 years and older, for all strains. Superiority of the immune response to each of the influenza B strains contained in Afluria Quadrivalent was shown in relativity to the antibody response after vaccination with TIV formulation not containing B lineage strains for subjects 18 years of age and older. Superiority against the alternate B strain was also demonstrated for each of the influenza B strains in both age subgroups: 18 through 64 years and 65 years and older.

In a randomized, comparator-controlled study that enrolled 1,250 subjects aged 18 through 64 years of age, the trivalent formulation of Afluria (influenza vaccine) administered by the PharmaJet Stratis needle-free injection system compared to administration of Afluria by needle and syringe demonstrated noninferiority in the immunogenicity population for all strains. Post-hoc analyses of immunogenicity by age showed that younger subjects (18–49 years) elicited higher immunological responses than older subjects (50–64 years).

In a randomized, observer-blinded, comparator-controlled trial conducted in the United States in 2,278 children 5–17 years of age, Afluria Quadrivalent demonstrated noninferiority to that of a comparator vaccine containing the same recommended virus strains.

Seqirus is part of CSL Limited (ASX: CSL), headquartered in Melbourne, Australia. The CSL Group of companies employs more than 20,000 people with operations in more than 60 countries.

Seqirus was established on July 31, 2015, following CSL's acquisition of the Novartis influenza vaccines business and its subsequent integration with bioCSL. As the second largest influenza vaccine provider in the world, Seqirus is a major contributor to the prevention of influenza globally and a transcontinental partner in pandemic preparedness.

Seqirus operates state-of-the-art production facilities in the United States, the United Kingdom, and Australia and manufactures influenza vaccines using both egg-based and cell-based technologies. It has leading R&D capabilities, a broad portfolio of differentiated products, and a commercial presence in more than 20 countries. For more information, visit www.seqirus.com and www.csl.com.

Based in Golden, Colorado, PharmaJet's mission is worldwide acceptance of PharmaJet® needle-free devices as a standard of care in the vaccine delivery market. PharmaJet's devices are also integral in the development of multiple novel pharmaceuticals. The innovative Stratis® device has U.S. FDA 510(k) marketing clearance, CE Mark, and WHO PQS certification to deliver medications and vaccines either intramuscularly or subcutaneously. In August 2014, the PharmaJet Stratis® device was cleared for delivery of an influenza vaccine to deliver needle-free flu shots. The Tropis® device for intradermal injections received authorization to apply the CE Mark in May 2016. The PharmaJet needle-free devices are safe, fast, and easy to use. They eliminate needle stick injuries, needle reuse, and cross-contamination, and help reduce sharps waste disposal. For more information, visit http://pharmajet.com/.

Intarcia and Numab Reach Key Milestone with Selection of Multispecific Development Candidate for Autoimmune Disease

Business Wire: September 14, 2017 – BOSTON, MA, U.S.A., and PFÄFFIKON, Switzerland – Intarcia Therapeutics, Inc., and Numab Therapeutics AG today announced the achievement of a key milestone in their ongoing development partnership—the selection of a multispecific antibody construct targeting autoimmune and inflammatory diseases. This delivery marks the first major milestone in the strategic relationship, established in the spring of 2015, and triggers a payment to Numab that will bring the total payments for this project to CHF 11.5 million to date.

This milestone, achieved by utilizing Numab's innovative discovery and optimization platform to identify a highly potent and selective antibody fragment candidate, also signals an important next step towards realizing the potential of combining Numab's antibody-based

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therapeutics with Intarcia's unique formulation and delivery technology—the Medici Drug Delivery System™, a proprietary subcutaneous delivery system that, once placed under the skin, utilizes an osmotic engine that allows drug within the mini-pump to be released in a steady, consistent fashion.

David Urech, Ph.D., CSO and co-CEO of Numab, stated, "Intarcia's advanced delivery and formulation technologies set a very high bar for drug developers. We are proud to have successfully generated a robust trispecific lead candidate for autoimmune disease that has met all predefined biophysical and pharmacological properties *in vitro* and in nonhuman primates, and that is ready for the subsequent stage of Intarcia's formulation development. We are also excited to announce the start of a CHF 30 million financing to accelerate the development of our own proprietary pipeline in cancer and autoimmune disease and move our main program to the clinical research stage."

"Intarcia is excited to take this next step in our autoimmune and inflammatory disease programs with Numab," said Kurt Graves, chairman, president, and CEO, Intarcia. "We're committed to spearheading disruptive innovation by leveraging our proprietary Medici Drug Delivery System. With this new milestone in our partnership, we now have several combination products in our pipeline that we believe can be uniquely optimized for delivery in our Medici system."

Founded in 2011, Numab develops a proprietary pipeline of multispecific biotherapeutics in immuno-oncology and immunology, and has discovery and development partnerships with Intarcia Inc., Ono Pharmaceutical Co., Ltd., Kaken Pharmaceutical Co., Ltd., and Tillotts Pharma AG. Numab's plug-and-play multispecifics platform allows for a highly rational and reproducible process that rapidly yields promising clinical candidates with new mechanisms of action, superior efficacy, and a favorable safety profile. For further information, visit www.numab.com.

Intarcia Therapeutics, Inc. is a biopharmaceutical company developing therapies to enhance treatment and prevention outcomes by optimizing and improving the efficacy, continuous administration, and tolerability of drug therapies. Delivering medicines just once or twice yearly to prevent and/or chronically treat diseases holds potential to improve outcomes by improving effectiveness over time and by addressing real-world unmet needs around poor patient adherence and persistence rates that are high in the majority of chronic diseases. Intarcia is investigating multiple therapies, including combination therapies, for chronic diseases leveraging the convergence of novel medicines and the proprietary Medici Drug Delivery System™. Intarcia is developing a strong pipeline in important therapeutic areas, including diabetes (ITCA 650), obesity, autoimmune diseases, HIV, and other serious disorders.

Bristol-Myers Squibb and Halozyme Enter Global Collaboration and License Agreement for Enhanze Technology

Business Wire: September 14, 2017 – NEW YORK, NY, and SAN DIEGO, CA, U.S.A. – Bristol-Myers Squibb Company (NYSE: BMY) and Halozyme Therapeutics, Inc. (NASDAQ: HALO) today announced a global collaboration and license agreement to develop subcutaneously administered Bristol-Myers Squibb immuno-oncology medicines using Halozyme's Enhanze® drug-delivery technology.

"We are excited to partner with Halozyme to pursue potential new approaches to how our medicines are delivered to patients," said Murdo Gordon, chief commercial officer, Bristol-Myers Squibb. "Through our work with Halozyme, we hope to improve the patient treatment experience by developing flexible and convenient treatment delivery options."

The Halozyme Enhanze technology is based on a proprietary recombinant human hyaluronidase enzyme (rHuPH20) that temporarily degrades hyaluronan—a glycosaminoglycan or chain of natural sugars in the body—to aid in the dispersion and absorption of other injected therapeutic drugs. This technology may allow for more rapid delivery of large-volume injectable medications, such as medications that are currently delivered intravenously, through subcutaneous delivery.

"Bristol-Myers Squibb has one of the industry's most advanced and extensive immuno-oncology portfolios with a clear commitment to patient-centered innovation," said Dr. Helen Torley, president and chief executive officer of Halozyme. "Through this collaboration we are excited to explore the potential for Enhanze to expand the number of cancer patients who may receive their therapies as a rapidly administered subcutaneous injection."

Under the terms of the agreement, Halozyme will receive an initial $105 million for access to the Enhanze technology. Bristol-Myers Squibb has designated multiple immuno-oncology targets including programmed death 1 (PD-1) and has an option to select additional targets within five years from the effective date. The collaboration may extend to a maximum of 11 targets. Halozyme has the potential to earn milestone payments of up to $160 million for each of the nominated collaboration targets and additional milestone payments for combination products, subject to achievement of specified development, regulatory, and sales-based milestones. In addition, Bristol-Myers Squibb will pay Halozyme royalties on sales of products using the Enhanze technology developed under the collaboration.

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The agreement is subject to customary anti-trust clearance by the U.S. Justice Department and Federal Trade Commission pursuant to the Hart-Scott-Rodino Act.

For Bristol-Myers Squibb, the transaction is expected to be dilutive to non-GAAP earnings per share (EPS) in 2017 and 2018 by approximately $0.01, and by approximately $0.05 in 2019.

Halozyme's proprietary Enhanze® drug-delivery technology is based on its patented recombinant human hyaluronidase enzyme (rHuPH20). rHuPH20 has been shown to remove traditional limitations on the volume of biologics that can be delivered subcutaneously (just under the skin). By using rHuPH20, some biologics and compounds that are administered intravenously may instead be delivered subcutaneously. Enhanze may also benefit subcutaneous biologics by reducing the need for multiple injections. This delivery has been shown in studies to reduce health care practitioner time required for administration and shorten time for drug administration.

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop, and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube, and Facebook.

At Bristol-Myers Squibb, patients are at the center of everything we do. Our vision for the future of cancer care is focused on researching and developing transformational immuno-oncology (I-O) medicines for hard-to-treat cancers that could potentially improve outcomes for these patients.

We are leading the scientific understanding of I-O through our extensive portfolio of investigational compounds and approved agents. Our differentiated clinical development program is studying broad patient populations across more than 50 types of cancers with 14 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs position us to advance the I-O/I-O, I-O/chemotherapy, I-O/targeted therapies, and I-O radiation therapies across multiple tumors and potentially deliver the next wave of therapies with a sense of urgency. We also continue to pioneer research that will help facilitate a deeper understanding of the role of immune biomarkers and how a patient's tumor biology can be used as a guide for treatment decisions throughout their journey.

We understand making the promise of I-O a reality for the many patients who may benefit from these therapies requires not only innovation on our part but also close collaboration with leading experts in the field. Our partnerships with academia, government, advocacy, and biotech companies support our collective goal of providing new treatment options to advance the standards of clinical practice.

Halozyme Therapeutics is a biotechnology company focused on developing and commercializing novel oncology therapies that target the tumor microenvironment. Halozyme's lead proprietary program, investigational drug PEGPH20, applies a unique approach to targeting solid tumors, allowing increased access of co-administered cancer drug therapies to the tumor in animal models. PEGPH20 is currently in development for metastatic pancreatic cancer, non-small cell lung cancer, gastric cancer, and metastatic breast cancer and has potential across additional cancers in combination with different types of cancer therapies. In addition to its proprietary product portfolio, Halozyme has established value-driving partnerships with leading pharmaceutical companies including Bristol-Myers Squibb for its Enhanze® drug delivery technology. Halozyme is headquartered in San Diego. For more information, visit www.halozyme.com.

Eos Biosciences Announces Issuance of U.S. Patent for Novel Oncology Theranostic

Business Wire: September 13, 2017 – LOS ANGELES, CA, U.S.A. – Biosciences, Inc., a bio-targeted nanomedicines company developing a novel nanoparticle drug delivery platform, with a proprietary oncology pipeline, announced that the U.S. Patent and Trademark Office has issued U.S. patent no. 9,757,386, which covers Eos Biosciences' theranostic product Eos-002, a HER3-targeted Eosome for the treatment and imaging of solid tumors. HER3 is overexpressed on many types of HER2+ metastatic and drug-resistant solid tumors, as well as triple negative breast cancer (TNBC).

This newly issued patent further enhances the company's intellectual property portfolio, which includes U.S. patent no. 9,078,927, covering Eos Biosciences' first proprietary product in preclinical development, Eos-001, with doxorubicin payload. The clinical development of Eos-001 is intended to address TNBC and HER2+ breast cancer resistant or nonresponsive to first line therapies.

Omar Haffar, Ph.D., founder, president, and chief executive officer, commented, "The allowance of this patent represents a significant milestone for Eos Biosciences, as we continue to build and strengthen our intellectual property portfolio." He continued, "We anticipate additional exciting IP developments in 2017, as we deepen our oncology presence and widen our therapeutic delivery coverage."

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Eos-002 is a HER3 targeted theranostic with a manganese corrole payload for treating and imaging solid tumors. Corroles are pophyrine-like macrocyclic compound that can incorporate metal ions. Corroles alter the function of mitochondria, leading to increased production of free radicals and subsequent cell death. When packaged into Eosomes, corroles were shown to have impressive effects on killing cancer cells *in vitro* and resolving tumor xenografts *in vivo*.

Eosomes are self-assembling nanobiologic particles composed of a recombinant polypeptide and a therapeutic payload. The recombinant polypeptide is designed to incorporate three functional domains for cell targeting, active endosomal escape, and therapeutic payload binding. The modular design of the polypeptide provides significant versatility in adapting the application of the Eosomes to multiple disease areas and therapeutic modalities.

Eos Biosciences, Inc., is a bio-targeted nanomedicines company based in Los Angeles, California, with world-wide, exclusive rights to a novel and innovative drug-targeting and delivery platform technology developed at Cedars-Sinai Medical Center in Los Angeles. The technology facilitates the effective delivery of approved and novel therapeutics to disease sites using the Eosomes nanobiologic particles.

DFB Pharmaceuticals Forms NanOlogy™ for Clinical Development of Naked Nanoparticle Platform to Treat Cancer and Related Illnesses

Business Wire: September 12, 2017 – FORT WORTH, TX, U.S.A. – DFB Pharmaceuticals, a private investment and development group, in collaboration with CritiTech and US Biotest, has formed NanOlogy to finance and develop a breakthrough technology platform to produce unique, patented, naked nanoparticle forms of paclitaxel and docetaxel for local delivery with the potential for greater efficacy and safety to treat cancer and other serious illnesses.

NanOlogy has developed sterile suspension forms of NanoPac® (nanoparticle paclitaxel) and NanoDoce® (nanoparticle docetaxel) as well as an inhaled form of NanoPac. A topical form identified as SOR007 (nanoparticle paclitaxel) ointment was developed by affiliate, DFB Soria, and licensed to NanOlogy for clinical development in oncology.

The sterile suspension has been designed to be injected directly into tumors, cysts, peritoneum, or other body cavities, where studies have demonstrated the nanoparticles remain and slowly release for four weeks, resulting in prolonged local exposure. In contrast, systemic forms of taxanes remain at the treatment site for a short time, as they are rapidly cleared from the body.

NanOlogy is progressing a broad clinical development program for NanoPac in 2017 that includes clinical trial evaluation of its sterile suspension in ovarian cancer (with orphan drug designation), prostate cancer, pancreatic cancer, and pancreatic mucinous cysts. In addition, clinical trial evaluation of SOR007 ointment is underway for actinic keratosis (under affiliate, Soria) and is expected to begin in the fourth quarter for cutaneous metastases. Clinical trials in various cancers are planned in 2018 for NanoDoce pending approval of its IND, and the inhaled version of NanoPac is in a preclinical efficacy study for lung cancer.

"Systemic administration of paclitaxel and docetaxel is associated with significant adverse effects. Physicians and scientists have known for decades that paclitaxel and docetaxel are effective cancer killing agents and have long searched for ways to preferentially retain high concentration of drug at the treatment site to increase efficacy," said Maurie Markman, M.D., president of medicine and science, Cancer Treatment Centers of America®. "The NanOlogy technology may offer a solution by enabling local delivery of large, sustained amounts of the drug at the site of disease and reducing systemic exposure and systemic side effects."

NanoPac and NanoDoce are manufactured by a patented nanoparticle production technology platform that reduces the size of unprocessed paclitaxel and docetaxel crystals by up to 400 times into stable, naked nanoparticles with an exponential increase in surface area and unique geometry. Unlike other nanoparticles, which require coating agents to keep them stable, the patented NanOlogy nanoparticles are stable in their naked form and suspended prior to use in simple vehicles without coating agents.

"We are excited about the potential of this technology platform to bring breakthrough therapies to patients with a wide range of cancers and other serious illnesses," commented H. Paul Dorman, chairman and CEO of NanOlogy.

NanOlogy, LLC (www.nanology.us) is a company formed by DFB Pharmaceuticals, LLC, of Fort Worth, Texas, CritiTech, Inc., of Lawrence, Kansas, and US Biotest, Inc., of San Luis Obispo, California, to finance and clinically develop a patented nanoparticle technology platform for local, sustained delivery of proven drugs aimed at increasing their safety and efficacy in the treatment of cancer and related conditions.

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DFB Pharmaceuticals, LLC (www.dfb.com) is a private Texas investment group with an entrepreneurial drive for developing new healthcare products and businesses. Founded in 1990, DFB and its principals have realized more than $1.5 billion in value through startups, strategic acquisition, and sale of companies and technologies, internal product development, brand optimization, and operations in the healthcare industry.

CritiTech, Inc. (www.crititech.com) is private Kansas particle engineering company focused on developing new drugs and improving existing drugs. Using the company's proprietary supercritical precipitation technology (SCP Technology) CritiTech specializes in optimizing the delivery of challenging drug substances, potent molecules, and poorly soluble compounds. In addition, CritiTech uses its SCP Technology to improve the efficacy, drug delivery options, dosing regimen, and pharmacokinetics of a wide variety of drugs, including oral, injectable, and inhaled drugs.

US Biotest, Inc., is a private California company dedicated to the development of therapeutics to address serious unmet medical needs. Building on strong relationships with industry experts, academic institutions, and leading physicians, the company provides product development strategy and support. US Biotest manages efficient delivery of programs from nonclinical through late-stage clinical trials.

Lipofoods to Raise the Bar with Natural, Sustained-Release Caffeine

PRNewswire: September 12, 2017 – BARCELONA, Spain – Lipofoods, SLU, launches Newcaff™ microcapsules, a natural, slow-release caffeine formulation for athletes and others living an active lifestyle. The company will introduce Newcaff microcapsules at SupplySide West, Las Vegas, September 28–29, 2017, at Stauber USA Inc.'s booth #J149.

Newcaff microcapsules is a novel delivery system designed to mask the bitter taste of caffeine and ensure controlled release, making it more affordable for food and beverage products targeting the active lifestyle.

Stauber is Lipofoods' distributor for North America, handling Newcaff microcapsules and Lipophytol® (a palm-free, water-dispersible phytosterol) as well as other advanced Lipofoods ingredients.

"Athletes seek natural solutions to increase their energy and maintain it for a longer time," explains Isabel Gomez, marketing manager for Lipofoods. "Newcaff was designed to help athletes as well as consumers living an active lifestyle. Formulating sports and nutrition products with caffeine poses big challenges in both flavor and sustained action. Newcaff microcapsules enable a clean taste of sustained- caffeine release."

According to research data from Innova Market Insights, there was a 19% rise in sports/recovery claims, and 14% for energy/alertness claims, from 2012 through 2016. These launches are increasingly targeting active lifestyles, moving outside traditional sports powders, drinks, and bars to feature in a wide range of mainstream categories.

In an *in vitro* study, the caffeine released from Newcaff microcapsules was tested following Health Canada's official method to determine the disintegration time during the digestion process. Newcaff microcapsules-60 and Newcaff microcapsules-75 showed good retention with improved sustained-release profiles compared to raw caffeine sources.

Newcaff microcapsules are available in two caffeine concentrations of 60% and 75%, providing different release profiles depending on customer preferences. The formula is ideal for food supplements, powders, bars, gels, chewables, milkshakes, and other food products. "Newcaff microcapsules enables our clients to create cleaner products since they don't have to add expensive flavors or additives to mask caffeine's bitter taste," explains Gomez.

Lipofoods, a Lubrizol Company, specializes in the development and production of microencapsulated functional ingredients, providing nutritional and technical solutions for the food, beverage, and dietary supplement industries.

The Gene Editing Institute of Christiana Care's Helen F. Graham Cancer Center & Research Institute Signs Agreement with ABS to Modify Cell Lines to Accelerate Cancer Therapies

Christiana Care Health System: September 12, 2017 – Wilmington, DE, U.S.A. – To accelerate the development of next-generation cancer therapies, the Gene Editing Institute of the Helen F. Graham Cancer Center & Research Institute at Christiana Care Health System has agreed to provide genetically modified cell lines to Analytical Biological Services, Inc. (ABS) of Wilmington, Delaware.

Under a three-year agreement, the Gene Editing Institute will act as sole provider of gene editing services and genetically modified cell lines to ABS for replication, marketing, and distribution to leading pharmaceutical and biomedical research companies worldwide.

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"This agreement with ABS will speed the progress in the discovery of effective cancer therapies and accelerate the path to prevention, diagnosis, and treatment of many forms of cancer," said Nicholas J. Petrelli, M.D., the Bank of America endowed medical director of the Helen F. Graham Cancer Center & Research Institute at Christiana Care Health System.

"This partnership greatly enhances our capability to provide the highest quality genetically engineered cells for drug discovery," said ABS president and CEO Charles Saller, Ph.D. "Our partners at the Gene Editing Institute are advancing molecular medicine, and their expertise adds a new dimension to our efforts to speed up drug discovery."

"One goal of The Gene Editing Institute is to develop community partnerships that can advance translational cancer research," said Eric Kmiec, Ph.D., founder and director of the Gene Editing Institute. "The Gene Editing Institute is driving innovation in gene engineering, and ABS has the know-how to grow and expand the cells in sufficient quantities, as well as to market them to pharmaceutical and biotechnology clients for drug screening and research."

The Gene Editing Institute is a worldwide leader in the design of the tools that scientists need to manipulate and alter human genetic material easier and more efficiently than ever before. Scientists at the Gene Editing Institute have designed and customized an expanding tool-kit for gene editing, including the renowned CRISPR-Cas9 system, to permanently disrupt or knock out genes, add or knock in DNA fragments, and create point mutations in genomic DNA. Last year, scientists at the Gene Editing Institute described in the journal *Scientific Reports* how they combined CRISPR and short strands of synthetic DNA to greatly enhance the precision and reliability of the CRISPR gene editing technique. Called excision and corrective therapy, or EXACT, this new tool acts as both a Band-Aid and a template during gene mutation repairs.

Genetically modified cells can help advance cancer research. By inactivating a single gene, scientists can test if it affects tumor formation or somehow alters the response to cancer therapies. Similarly, inserting a gene into a cell can produce a gene product that is a target for potential new drugs.

"Gene editing and the CRISPR technology is having a major impact on anticancer drug development because it allows us to validate the target of the candidate drug," said Dr. Kmiec. "Pharmaceutical companies want to use gene editing tools to identify new targets for anti-cancer drugs and to validate the targets they already have identified."

The Delaware BioScience Association helped connect the Gene Editing Institute with ABS. "The collaborative agreement between the Gene Editing Institute and ABS exemplifies the power of building a strong biotech community, flourishing further innovation, and keeping businesses engaged and thriving in the state of Delaware," said Helen Stimson, president and CEO of The Delaware BioScience Association. "The Delaware BioScience Association is committed to fostering meaningful relationships, such as this one, among its members and establishing strategic partnerships that bolster the state's innovation economy," she said.

"This is one of those times when the forces of nature align to bring two perfectly matched skill sets together," said Dr. Kmiec. "There is no question that our collaboration with ABS will accelerate the pace of drug discovery around the world."

Gecko Biomedical Receives CE Mark Approval for Setalum™ Sealant

Business Wire: September 11, 2017 – PARIS, France – Gecko Biomedical ("Gecko"), a medical device company developing innovative polymers to support tissue reconstruction, announced today that it has received CE Mark approval for its Setalum™ sealant, allowing the company to market its technology in Europe.

Setalum™ sealant is a biocompatible, bioresorbable, and on-demand activated sealant usable in wet and dynamic environments as an add-on to sutures during vascular surgery. The polymer is applied to tissue *in situ* and activated using a proprietary light activation pen.

The technology at the foundation of the Setalum™ sealant was developed at The Massachusetts Institute of Technology, Harvard Medical School, and Brigham and Women's Hospital. Setalum™ sealant is the most recent successful example of bio-inspired technology in medicine and is based on the adhesive mechanisms found in nature that work in wet and dynamic environments.

The grant of the CE Mark for the vascular sealant is the first regulatory validation of the safety and performance of Gecko Biomedical's scalable and innovative polymer platform.

"The Setalum™ sealant can be precisely and easily applied thanks to its viscosity and hydrophobicity and then activated at will to provide an instant hermetic barrier and effective hemostasis. The key features of this polymer technology were selected with physicians

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and patients in mind, and significantly improves upon the latest generation of hemostatic agents to become a gold standard in vascular surgery," said Jean-Marc Alsac, M.D., Ph.D., vascular surgeon at the Hôpital Européen Georges Pompidou in Paris, France, and the principal investigator of Gecko Biomedical's BlueSeal clinical study.

The BlueSeal clinical study was a prospective, single-arm and multi-center clinical investigation performed at four French university hospitals and undertaken in patients necessitating a carotid endarterectomy. Performance of the sealant was evaluated by the percentage of immediate hemostasis following clamp removal. Based on a sequential Bayesian design, the recruitment was stopped at 22 enrolled patients given the fulfilled performance criteria and the optimal safety profile of the sealant. Immediate hemostasis was achieved in 85% of patients, and all recorded adverse events were found to be representative of those commonly occurring in patients necessitating vascular reconstruction with none considered as related to the sealant.

Christophe Bancel, Gecko's CEO, said, "We are delighted to receive the CE Mark for our first product, Setalum™ sealant, as this will allow us to bring new and innovative solutions to the market to improve patient care. As a result, we are now ramping up our manufacturing capabilities and selection of strategic partners to bring this innovation to patients."

The company is swiftly expanding its applications, targeting new functionalities and tissue types to develop solutions for new clinical indications and geographic markets.

"Our ability to bring an entire new family of innovative polymers from the bench to the bedside in less than two and a half years is a testimony of the versatility and scalability of our platform. We are now ready to fully expand, internally and through partnerships, into new therapeutic areas to design disruptive surgical solutions for patients," Bancel added.

Gecko Biomedical is a privately owned medical device company based in Paris, France, that is dedicated to the rapid development and commercialization of a unique biopolymer platform to address various unmet clinical needs.

The company's platform is based on a proprietary polymer family with unique properties including superior biocompatibility, tunable bioresorbability, and adjustable tissue adherence. Furthermore, the polymer hydrophobicity, high viscosity, and controlled "on demand" curing enables a unique and controlled delivery to targeted tissues or the creation of scaffolds.

Gecko Biomedical's first product, Setalum™ sealant, is an innovative polymer dedicated for tissue reconstruction. It is targeted to vascular reconstruction as an initial indication. Its structure is tunable, allowing customization for various applications and tissue types. The polymer is part of a biopolymer platform family that is fully industrialized and highly versatile, with potential novel applications in other fields of tissue reconstruction such as guided tissue repair and in the field of localized drug delivery.

The company's technology is based on world-class research and intellectual property from the laboratories of Prof. Robert Langer (MIT) and Prof. Jeffrey M. Karp (Brigham and Women's Hospital), who co-founded the company in 2013, alongside Christophe Bancel and Bernard Gilly from the iBionext Network. For more information, please visit www.geckobiomedical.com.

Lyndra, Inc., and Allergan Sign a Partnership to Develop Ultra-Long-Acting Oral Products

Business Wire: September 7, 2017 – WATERTOWN, MA, U.S.A. – Lyndra, Inc. (Lyndra) announced today a partnership with Allergan plc to develop orally administered ultra-long-acting (once-weekly) products for the treatment of Alzheimer's disease. The basis of the collaboration between the Boston-based startup and Allergan is Lyndra's innovative sustained-release technology, which has the potential to transform drugs typically dosed daily to once-weekly oral dosing.

Allergan and Lyndra will collaborate to develop ultra-long-acting formulations of Allergan's proprietary treatments for Alzheimer's disease, where caregiver burden and patient adherence are common challenges. By decreasing patients' overall pill burden and increasing adherence, novel, long-acting therapies have the potential to decrease overall healthcare costs and improve patient health outcomes.

"I am delighted that we have the opportunity to work so closely with the scientific team at Allergan to bring caregiver and patient innovation to this critical illness," said Amy Schulman, chief executive officer at Lyndra. "The chance to minimize the struggle with the daily pill can make a real difference to patients and their caregivers, ease the burden of medication compliance, and simplify the day-to-day challenges of chronic conditions. As a team, we at Lyndra are deeply committed to making a difference in how people get well, and our ultra-long-acting sustained release technology is built on the premise that a once-weekly oral pill will make a real difference in disease treatment and prevention."

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"As a leader in Alzheimer's treatment, Allergan is committed to developing new approaches that further reduce the burden of treatment for patients and their caregivers," said Sesha Neervanan, senior vice president of pharmaceutical development at Allergan. "In addition to its potential application in Alzheimer's disease treatment, we are excited by the potential for these technologies that could unlock a paradigm shift in the treatment of other conditions where less frequent administration is critical to improving compliance and patient care."

The Lyndra technology is a novel dosage form designed to temporarily reside in the stomach for up to one week while delivering a drug or combination of drugs, until its finely tuned components break apart and pass through the GI tract. By permitting sustained gastric residence, the technology could improve pharmacokinetic profiles by blunting peak and trough concentrations, and enable local GI delivery and less frequent patient dosing. Dr. Robert Langer, Institute Professor at MIT and co-founder of Lyndra, shared, "The astounding reality is that while there are so many effective, life-saving treatments available, nearly 50% of patients don't adhere to their medication regimens, which leads to avoidable negative health outcomes and premature deaths. We are delighted that Allergan shares in our vision of developing novel, long-acting technologies that transform how patients take medicine and take full advantage of available treatments."

In addition to the Allergan partnership, the company recently announced a five-year grant from the NIH to develop ultra-long-acting products for HIV. Catherine Reynolds, who recently joined as chair of Lyndra's Board of Directors, commented, "Lyndra's dedication to targeting unmet needs in diseases such as Alzheimer's is extraordinary. My enthusiasm as chair of Lyndra stems from the ability to improve public health outcomes and Lyndra's willingness to tackle the intractable issue of compliance."

As part of the transaction, Allergan may elect an additional compound, from any therapeutic category, for inclusion in the collaboration. The agreement provides a $15 million upfront payment to Lyndra along with up to $90M in development and regulatory milestones spread across the Alzheimer's program and the additional compound program. The transaction with Allergan is the largest deal to date harnessing Lyndra's pioneering work in the area of ultra-long-acting oral delivery and follows Lyndra's series A of $23 million announced this spring.

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

Pulmatrix Licenses Inhaled COPD Drug PUR0200 to Vectura Group plc

PRNewswire: September 6, 2017 – LEXINGTON, MA, U.S.A. – Pulmatrix, Inc. (NASDAQ: PULM), a clinical stage biopharmaceutical company developing innovative inhaled therapies to address serious pulmonary diseases, today announced that it has partnered with Vectura Group plc (LSE: VEC) ("Vectura") to develop Pulmatrix's drug candidate, PUR0200, for chronic obstructive pulmonary disease (COPD) for the U.S. market. Vectura and/or its partners will be responsible for all future development costs to advance the product for the United States.

Pulmatrix will provide the data package for PUR0200 and assist with the transfer of development and manufacturing activities to Vectura. As part of the agreement, a technology access fee of $1 million will be payable to Pulmatrix upon successful achievement of pre-agreed pharmaceutical development criteria. Vectura will commence development immediately and will pay Pulmatrix a mid-teen percentage share of any future revenues that Vectura receives relating to future development and sale of PUR0200 and PUR0200-related products including future combinations.

"Vectura has deep experience with inhaled drugs and innovative dry powder delivery technologies, which makes them an optimal partner to advance PUR0200 as a better product for COPD patients," explained Robert W. Clarke, Ph.D., chief executive officer of Pulmatrix. "By out-licensing the program to Vectura, PUR0200 is in the hands of a partner with a demonstrated ability to develop drugs for COPD and allows Pulmatrix to focus on our product pipeline including PUR1900 and PUR1800."

PUR0200 combines tiotropium bromide, the active component in the billion-dollar blockbuster drug Spiriva, with Pulmatrix's ground-breaking iSPERSE™ drug delivery platform. Early stage clinical trials of PUR0200 have shown the product to be up to five times more efficient at delivering the drug to the lungs than the currently marketed product. Vectura will utilize its innovative dry power inhaler device technology to deliver PUR0200, with the goal of providing enhanced delivery and a better device format of PUR0200 for patients.

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Pulmatrix is a clinical-stage biopharmaceutical company developing innovative inhaled therapies to address serious pulmonary disease using its patented iSPERSE™ technology. The company's proprietary product pipeline is focused on advancing treatments for rare diseases, including PUR1900, an inhaled anti-fungal for patients with cystic fibrosis (CF) and severe asthma, and PUR1800, a narrow spectrum kinase inhibitor for patients with COPD. In addition, Pulmatrix is pursuing opportunities in major pulmonary diseases through collaborations, including PUR0200, a branded generic in clinical development for COPD. Pulmatrix's product candidates are based on iSPERSE™, its proprietary dry powder delivery platform, which seeks to improve therapeutic delivery to the lungs by maximizing local concentrations and reducing systemic side effects to improve patient outcomes.

PUR0200 is Pulmatrix's once-daily, inhalable iSPERSE™ reformulation of tiotropium bromide for COPD patients. PUR0200 is a branded alternative to Spiriva® HandiHaler® in the United States.

Vectura, a FTSE250 company listed on the London Stock Exchange (LSE: VEC), is an industry-leading device and formulation business for inhaled airways products offering a uniquely integrated inhaled drug delivery platform. With its extensive range of device and formulation technologies, integrated capabilities, and collaborations, it is a leader in the development of inhalation products, increasing its ability to help patients suffering from respiratory diseases.

PKU: Preclinical Kinetic Data Showing Prolonged Release of Amino Acids Thanks to the Innovative Physiomimic Technology by APR Presented at the 13th ICIEM Congress

Business Wire: September 5, 2017 – BALERNA, Switzerland – APR Applied Pharma Research s.a. ("APR"), the Swiss independent developer of science driven and patent protected healthcare products, announced today the results of a preclinical kinetic study showing a physiological absorption of clinically relevant groups of amino acids (AAs) thanks to the application of the patented Physiomimic™ drug delivery technology platform. APR's innovative product is intended to be used for the management of patients with phenylketonuria (PKU).

The results of the investigation indicate that the Physiomimic™ technology by APR is able to modify the release of clinically relevant AAs by lowering and retarding their absorption profiles if compared to the same mix of amino acids without the application of the technology. Also remarkable is that the kinetic profile of the AAs engineered with the Physiomimic™ technology resembles that of casein—a reference food protein known to have a prolonged absorption profile.

The study suggests that APR's advanced formulation of AAs has the potential of contributing to maintain phenylalanine (PHE) levels within the recommended ranges, with less prominent fluctuations of PHE levels over time, thanks to a prolonged release of the AAs in the gut, which is thought to allow a more efficient utilization of the absorbed amino acids, PHE included. Furthermore, the Physiomimic™ technology has the ability of remarkably masking their taste and odor, with potential positive consequences on aftertaste for an exceptionally palatable product.

The outcome of the preclinical study will be presented in an oral presentation ("Gut Microbiota and Human Metabolism," Thursday, September 7, 2017, 11:00–12:30) during the 13th International Congress of Inborn Errors of Metabolism in Rio de Janeiro on September 5–8, 2017 (ICIEM 2017). A poster will also illustrate the results of the application of the innovative Physiomimic™ technology (attended poster session Wednesday, September 6, 17:30–20:00) to amino acids for PKU.

"For the first time, the application of a pharmaceutical drug delivery technology platform to a medical food leads to a real change in PKU management," Paolo Galfetti, CEO of Applied Pharma Research, stated. "Since data show that there are still open issues in the management of PKU, we developed the Physiomimic™ technology with the aim of meaningfully contributing to fulfill significant unmet needs of this disorder, providing patients, healthcare professionals (HCPs), and care givers with a product that would deliver amino acids in a physiological manner, whilst being very palatable and thus significantly improving patient compliance."

"The development plan to characterize our innovative product for PKU is robust," added Giorgio Reiner, corporate director R&D of Applied Pharma Research, "with the next major step being a clinical kinetic study in human volunteers as a proof of concept of the prolonged release of amino acids and their consequent physiological absorption. Other preclinical studies as well as clinical evidences will reinforce the scientific profile of our proprietary technology and product to help us continue this journey."

On October 5–8, APR will also sponsor the 31st E.S. PKU Conference (European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria), in Hell, Norway, continuing to contribute to the advancement of the management of this rare disorder.

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APR is a Swiss independent developer of science-driven, patent-protected healthcare products. The company identifies, develops, and licenses science-driven, value-added products designed to address patient or consumer needs in selected therapeutic areas on a global basis. In particular, APR is currently focused on two areas: (1) internally developed and financed (alone or together with our co-development partners) proprietary, value-added products to be licensed to healthcare companies for their commercialization, and (2) support to third party projects by offering added-value R&D services under contract and fee-for-service arrangements. APR has a balanced pipeline of revenue generating branded products marketed in all major markets combined with a compelling pipeline of products at different stages of development. APR has entered into licensing and partnership agreements with pharmaceutical companies in over 70 countries with international sales on a worldwide basis.

Phenylketonuria or PKU is a rare, genetic, recessive metabolic disorder affecting about 50,000 people worldwide. PKU is characterized by the deficiency or the malfunctioning of a liver enzyme needed to process phenylalanine (PHE), an essential amino acid found in most protein-containing food. Excessive amounts of PHE in the bloodstream become toxic to the brain, impairing the normal development of the central nervous system. If not properly treated, PKU leads to severe, non-recoverable mental retardation and major cognitive disabilities. PKU can only be treated through a strict, life-long, low-protein (low-PHE) dietetic treatment combined with a daily assumption of low-protein modified foods and medical food that provides PHE-free amino acids and other important nutrients needed due to the dietary restrictions of PKU patients.

For more information about Physiomimic™ technology, please visit www.apr.ch/apr-pharma-products/medical-prescription/genetic-metabolic-disease. For press releases and other company information, visit www.apr.ch.

August

PureTech Health Exclusively Licenses Glyph Technology from Monash University to Harness Lymphatic Biology

Business Wire: August 29, 2019 – BOSTON, MA, U.S.A. – PureTech Health plc ("PureTech Health" or the "company", LSE: PRTC), an advanced, clinical-stage biopharmaceutical company, today announced an exclusive licensing agreement with Monash University for a lymphatic targeting platform (the Glyph technology) based on the pioneering research of Christopher Porter, Ph.D., director of the Monash Institute of Pharmaceutical Sciences (MIPS) at Monash University in Australia. The Glyph technology is aimed at harnessing the biology of the lymphatic system to develop novel therapeutics, including those that selectively target certain lymph nodes. This program further builds on PureTech's leadership in identifying novel approaches to address dysfunctions of the brain, immune, and GI systems.

"The lymphatic system is a vastly underexplored circulatory network that serves a fundamental role in maintaining physiological homeostasis and immune control," said Dr. Joseph Bolen, chief scientific officer of PureTech Health. "The Glyph technology represents a major advancement in potentially enhancing transport and distribution of therapeutics via the lymphatic system and targeting of certain lymph nodes. By addressing the immune system at the sites of dysregulation and immune control, this novel approach has the potential to radically transform the treatment of serious disease."

By virtue of its architecture and distribution throughout the body, the lymphatic system potentially represents a key conduit for communicating signals at the intersection of the immune-gut-brain axis. The Glyph technology is designed to harness the biology of the lymphatic system and the endogenous trafficking of compounds through this network to develop novel drugs that bypass first-pass metabolism, improve oral bioavailability, and significantly lower the risk of liver toxicity. In particular, the mesenteric lymph nodes, proximal to the gut, are exposed to a host of microbiome-related species and serve an integral role in immune education and control. Targeting the lymphatic pathway potentially enables rational design of therapeutics to modulate the immune system, representing an innovative approach to treating a broad range of serious immunological disorders, such as cancer and autoimmune diseases. The Glyph technology will be developed by PureTech Health through its subsidiary, Glyph Biosciences, in collaboration with Dr. Porter's laboratory.

"Through our work at Monash University, we have designed chemistries that potentially enable drugs to be preferentially and effectively transported through the endogenous pathways of lipid transport via the intestinal lymphatics in a controlled manner," said Dr. Porter. "Our technology has been shown in preclinical experiments to achieve significant oral bioavailability of compounds through the avoidance of first-pass metabolism, and has the potential to significantly mitigate liver toxicity and to alter systemic drug disposition. I am excited to be working with PureTech Health to rapidly advance this potentially disruptive technology platform toward the development of novel therapeutics."

"This new program builds on PureTech's unique expertise and approach to utilize novel biology, such as the lymphatic distribution network, to treat serious diseases," said David Steinberg, chief innovation officer and a cofounder of PureTech Health. "We look

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forward to a great partnership with Dr. Porter and building on his work at Monash University to drive advancements in immunomodulation."

PureTech Health (PureTech Health plc, PRTC.L) is an advanced, clinical-stage biopharmaceutical company developing novel medicines targeting serious diseases that result from dysfunctions in the immune, nervous, and gastro-intestinal systems by intervening early and addressing the underlying pathophysiology of disease. The company is advancing a rich pipeline that includes two pivotal or registration studies expected to read out in 2017, multiple human proof-of-concept studies, and several early clinical and preclinical programs. PureTech Health's growing research and development pipeline has been developed in collaboration with some of the world's leading scientific experts, who along with PureTech's experienced team and a stellar Board identify, analyze, and advance very selectively the opportunities the company believes hold the most promise for patients. This experienced and engaged team places PureTech Health at the forefront of groundbreaking science and technological innovation and leads the company between and beyond existing disciplines. For more information, visit www.puretechhealth.com or connect with us on Twitter @puretechh.

Sorrento Therapeutics, Inc., Submits NDA for ZTlido™ Next-Generation Lidocaine Patch

PRNewswire: August 29, 2017 – SAN DIEGO, CA, U.S.A. – Sorrento Therapeutics, Inc. (NASDAQ: SRNE) ("Sorrento"), announced today that Scilex Pharmaceuticals Inc. ("Scilex"), a majority-owned subsidiary of Sorrento, resubmitted the NDA and responded to all of FDA comments related to the initial NDA submission for its lead product candidate, ZTlido™ (lidocaine patch 1.8%).

ZTlido is a next-generation non-opioid, lidocaine patch currently in development for the relief of pain associated with post-herpetic neuralgia (PHN), a severe neuropathic pain condition.

ZTlido anhydrous patch is based on a novel and proprietary technology that delivers bioequivalent levels of lidocaine to Lidoderm® (lidocaine patch 5%), which has been confirmed in two separate clinical studies. Scilex has also confirmed bioequivalence between ZTlido and Versatis® (lidocaine medicated plaster 5%), which is the European brand name for the comparator product. A clinical adhesion study demonstrated that greater than 90% of the subjects had greater than 90% adhesion over the 12 hour administration period using an FDA-recommended five-point scale. In a separate clinical study, ZTlido demonstrated strong adhesive properties even during moderate exercise with no meaningful impact on pharmacokinetics.

The novel technology allows ZTlido to achieve the ability to deliver a bioequivalent therapeutic dose of lidocaine for the treatment of PHN pain, but does so with a drug load of 36 mg/patch versus 700 mg/patch for Lidoderm and Versatis. This biopharmaceutic efficiency leads to an approximate 30-fold reduction in residual drug in ZTlido after use compared to Lidoderm and Versatis, which can significantly reduce safety risks to children and pets, and presents less drug waste entering the environment when discarded after use.

"We are excited about the opportunity to bring to the market a product that will adhere during the full prescribed treatment period as well as be able to be worn during exercise," said Anthony Mack, president of Scilex Pharmaceuticals. "As a company, our desire is to help patients by developing better products to treat pain."

"The state-of-the-art manufacturing technology used for ZTlido production enables high drug delivery efficiency with strong adhesive properties. The thought behind this lidocaine patch product exemplifies Sorrento's commitment to bringing life-enhancing therapies to patients in need," said Dr. Henry Ji, chairman and CEO of Sorrento.

If the NDA is accepted by the FDA, the review clock could be six months. If approved, ZTlido could be ready for commercial launch in the United States in 2018.

The company intends to submit a marketing authorization application for ZTlido in Europe in the fourth quarter of this year. Total 2016 sales of currently approved prescription lidocaine patches, in the United States and Europe, were approximately $750 million, and we expect ZTlido to be a significant player in the market.

Enteris BioPharma Doses First Woman in Phase 2a Clinical Trial of Ovarest™ (Oral Leuprolide Tablet) for Endometriosis

PRNewswire: August 24, 2017 – BOONTON, NJ, U.S.A. – Enteris BioPharma, Inc., a biotechnology company developing innovative drug products built around its proprietary delivery technologies, announced today that the first woman has been dosed in its phase 2a clinical trial to evaluate Ovarest™, an oral formulation of leuprolide, for the treatment of endometriosis. Ovarest™ was developed utilizing Enteris's proprietary Peptelligence™ platform, a novel formulation technology that enables oral delivery of molecules that are typically injected, including peptides and BCS class II, III, and IV small molecules.

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Ovarest™ represents Enteris's most clinically advanced internal product candidate and underscores Enteris's rapidly advancing clinical development pipeline targeting underserved patient populations in women's health. The phase 2a trial is designed as a randomized, open-label, parallel-group, active-control phase 2a pharmacokinetics (PK)/pharmadynamics (PD) study in 32 healthy female volunteers. The study will determine the safety and evaluate the PK/PD metrics of two different oral doses of Ovarest™ in comparison to the leuprolide formulation approved for the treatment of endometriosis, Lupron Depot® 3.75 mg, a monthly intramuscular injection.

"Initiation of the Ovarest™ phase 2a clinical trial is a significant milestone for Enteris and underscores our commitment to building an internal product pipeline of innovative oral therapeutics that address underserved medical needs in women's health," said Joel Tune, chief executive officer and executive chairman of Enteris BioPharma. "Endometriosis affects nearly six million women in the United States, and there have been few advancements in the space to provide these women with more patient-friendly treatment options. Ovarest™ has the potential to become a high-value and broadly adopted therapeutic for the treatment of endometriosis, and together with Tobrate™, demonstrates the capabilities of our Peptelligence™ platform to transform currently available injectable drugs into patient-friendly oral formulations."

Since its founding in 2013, Enteris BioPharma has advanced multiple internal and external programs leveraging its Peptelligence™ platform. The technology has been developed and proven effective over the last decade to enable the safe delivery of peptide-based therapeutics and other molecules with low oral bioavailability. In addition to its internal development pipeline, Enteris's oral peptide delivery technology is the subject of several active external development programs, the most advanced of which include Tarsa Therapeutics' TBRIA, an oral calcitonin for patients with postmenopausal osteoporosis, and Cara Therapeutics' CR845, a potent peripheral kappa opioid receptor agonist. In January 2017, Enteris entered into separate agreements with Sanofi, Ferring Pharmaceuticals, and KeyBioscience AG (a fully owned subsidiary of Nordic Bioscience) to develop oral tablet formulations of peptide therapeutics owned by each company.

Enteris BioPharma, Inc., is a privately held, New Jersey-based biotechnology company offering innovative formulation solutions built around its proprietary drug delivery technologies. The company's proprietary oral delivery technology—Peptelligence™—has been the subject of numerous feasibility studies and active development programs, several of which are in late-stage clinical development. Additionally, Enteris BioPharma is advancing an internal product pipeline of oral tablet reformulations of drug products that address significant treatment opportunities for which there is no oral delivery option. Enteris BioPharma's most advanced internal product candidate, Ovarest™ (oral leuprolide tablet), is an oral peptide being developed for the treatment of endometriosis. For more information on Enteris BioPharma and its proprietary oral delivery technology, please visit www.EnterisBioPharma.com.

SynAgile Corporation Announces Closing of $10.4M Financing

PRNewswire: August 24, 2017 – WILSON, WY, U.S.A. – SynAgile Corporation (www.synagile.com), a privately held pharmaceutical company that develops and commercializes drug delivery systems using its proprietary OraFuse™ technology platform, today announced the closing of a $10.4 million round of equity investment. The round was led by affiliates of TAMCAP LLC. The proceeds will be used to conduct the first-in-human, phase 2 clinical trial of SynAgile's DopaFuse™ delivery system. The DopaFuse™ delivery system is the first noninvasive, continuous levodopa-carbidopa delivery system for the treatment of motor fluctuations associated with Parkinson's disease.

SynAgile is a biopharmaceutical company focused on developing and commercializing transformative therapeutics using its proprietary OraFuse™ noninvasive, continuous, oral dosing technology, with an initial focus on treating debilitating motor complications in patients with Parkinson's disease using its DopaFuse™ levodopa-carbidopa delivery system.

OraFuse and DopaFuse are trademarks of SynAgile Corporation. For more information, please visit SynAgile Corporation (www.synagile.com).

Titan Pharmaceuticals Receives FDA Clearance to Begin Clinical Study of Parkinson's Disease Treatment

PRNewswire: August 24, 2017 – SOUTH SAN FRANCISCO, CA, U.S.A. – Titan Pharmaceuticals, Inc. (NASDAQ: TTNP) announced today that the U.S. Food and Drug Administration (FDA) has cleared the Investigational New Drug (IND) application for its ropinirole implant intended for treatment of the signs and symptoms of Parkinson's disease. The phase 1/2 clinical study in patients will commence shortly.

"New treatments that offer continuous delivery of medication providing nonpulsatile stimulation of dopamine receptors in the brain appear to have some advantages over oral formulations," said Dr. Aaron Ellenbogen of the Michigan Institute of Neurological Disorders and the principal investigator at the first trial site, near Detroit, Michigan. "The ProNeura implants with ropinirole could

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potentially offer an important treatment option for continuous drug delivery that overcomes the fluctuating drug levels associated with oral administration of ropinirole, and we look forward to conducting this study."

The ropinirole implant, developed utilizing Titan's ProNeura™ technology, is designed for the long-term, continuous delivery of ropinirole HCl for the treatment of signs and symptoms of Parkinson's disease, including stiffness, tremors, muscle spasms, and poor muscle control. Ropinirole is a dopamine agonist currently available in daily or more frequently dosed oral formulations for the treatment of Parkinson's disease symptoms and restless leg syndrome.

The trial is an open-label, sequential, dose escalation study that will enroll approximately 20 subjects with idiopathic Parkinson's disease across three or more U.S. research sites. The primary objectives are to characterize the pharmacokinetic profile of the ropinirole implants, to evaluate their safety and tolerability, and to explore potential signals of efficacy using established disease-specific assessment scales. Patients on a stable dose of L-dopa plus oral ropinirole will have their oral ropinirole switched to ropinirole implants for three months of treatment.

"While oral formulations of ropinirole have greatly benefitted those suffering from Parkinson's disease, many patients develop serious motor complications and dyskinesias after several years, due to the peak-trough fluctuations of medication in the blood," said Kate Beebe, Ph.D., executive vice president and chief development officer at Titan. "Our ropinirole implant is designed to provide continuous, nonfluctuating therapeutic levels of medication for up to three months, potentially offering patients and clinicians a more effective treatment option. We thank the FDA for their timely review and comments on the IND and clinical protocol."

Titan Pharmaceuticals Inc. (NASDAQ: TTNP), based in South San Francisco, CA, is developing proprietary therapeutics primarily for the treatment of serious medical disorders. The company's lead product is Probuphine®, a novel and long-acting formulation of buprenorphine and the first and only commercialized treatment of opioid dependence approved by the U.S. Food and Drug Administration to provide continuous, around-the-clock blood levels of buprenorphine for six months following a single procedure. Probuphine employs Titan's proprietary drug delivery system ProNeura™, which is capable of delivering sustained, consistent levels of medication for three months or longer. Titan has granted commercial rights in the United States and Canada for Probuphine to Braeburn Pharmaceuticals. The ProNeura technology has the potential to be used in developing products for treating other chronic conditions such as Parkinson's disease and hypothyroidism, where maintaining consistent, around-the-clock blood levels of medication may benefit the patient and improve medical outcomes. For more information about Titan, please visit www.titanpharm.com.

Teikoku Pharma USA Announces Positive Topline Results from Phase 2 Clinical Trial of TPU-006 Nonopioid Pain Management Patch in Bunionectomy Surgery

PRNewswire: August 22, 2017 – SAN JOSE, CA, U.S.A. – Teikoku Pharma USA, Inc. (Teikoku Pharma) today announced positive topline results from its phase 2 proof of concept study of TPU-006, a 3-day dexmedetomidine transdermal patch, a novel drug delivery system with a nonopioid active moiety for the management of postsurgical pain. The preliminary results demonstrate that the patch provides effective pain control across several parameters and produced no unexpected safety events in a postoperative setting.

The double-blind, placebo-controlled, single-dose study evaluated the analgesic efficacy and safety of TPU-006 after bunionectomy surgery. A total of 87 patients had patches applied (either active or placebo).

Treatment with TPU-006 showed statistically significant key findings for lower pain scores and reduced use of opioid rescue medication compared with placebo, over the course of the study. TPU-006 was well tolerated, with no unexpected serious adverse events, minimal to no application site skin irritation, or drowsiness. Patients treated with TPU-006 experienced less constipation and nausea due to reduced use of opioid rescue medication.

"TPU-006 offers the potential to improve current postoperative or chronic pain management practices. It also provides a much-needed strategy to reduce the use of narcotic painkillers. The ease of administration (application and removal), as seen in this study, means that the TPU-006 patch can be used in both the inpatient and outpatient setting," said Jutaro Shudo, chief science officer of Teikoku Pharma.

"We are pleased to see the efficacy of TPU-006 in this well-controlled phase 2 study. As the pace of the opioid epidemic continues to increase, we believe TPU-006 may help reduce the dependency on opioid-based medications following surgery," added Paul Mori, president and chief executive officer of Teikoku Pharma.

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TPU-006 is an investigational transdermal product, intended to deliver dexmedetomidine for up to several days from a single application. Dexmedetomidine is a selective α2-adrenergic agonist, which is part of a family of agonists that are frequently used for sedation, muscle relaxation, and analgesia. Dexmedetomidine is commercially available as Precedex® (dexmedetomidine hydrochloride) injection for intravenous use.

The global pain market was valued at $28.6 billion in 2010 and is projected to increase at a 3% CAGR to $35.1 billion in 2017. It has huge growth potential due to an increase in the aging population (2% in the United States). The postoperative pain market has been projected to be approximately one-fifth of the total market ($5.9 billion).

Teikoku Pharma USA, Inc., is located in San Jose, California, a wholly owned subsidiary of Teikoku Seiyaku Co., Ltd., of Japan. This international specialty pharmaceutical company is focused on developing novel best-in-class treatment solutions to address some of the biggest unmet patient needs. It develops and manufactures pharmaceutical products based on proprietary delivery platform technologies. Teikoku Pharma's main products include: Lidoderm® (lidocaine 5% patch) for postherpetic neuralgia (distributed by Endo Pharmaceuticals in the United States and Grunenthal GmbH in Europe and Latin America as Versatis®) and docetaxel alcohol-free injection (distributed by Eagle Pharmaceuticals in the United States).

A Plant-Based Delivery System for Anticancer Drugs

PRNewswire: August 18, 2017 – WASHINGTON, DC, U.S.A. – An article published in *Experimental Biology and Medicine* (volume 242, issue 14, August 2017) reports that a plant virus–based system can be used to deliver anticancer drugs. The study, led by Dr. Nicole Steinmetz in the Department of Biomedical Engineering at the Case Western Reserve University Schools of Engineering and Medicine in Cleveland, Ohio, demonstrates that a complex consisting of tobacco mosaic virus and vcMMAE, a first-line chemotherapy agent for the treatment of lymphoma, can kill cancer cells.

Over 800,000 Americans are living with or in remission from lymphoma, a cancer of the lymph system. Non-Hodgkin's lymphoma (NHL) is the most common type of lymphoma, and patients with this disease have a poor prognosis. The first-line treatment strategy for NHL is chemotherapy. However, this approach is associated with off-target side effects. Nanocarriers are being developed to improve drug delivery and minimize off-target effects associated with anticancer drugs. However, the utility of many of these systems in drug delivery may be limited by their spherical shape. Elongated nanomaterials may be superior to their spherical counterparts due to increased target cell interactions and decreased immune cell uptake. Nonetheless, the synthesis of highly uniform elongated nanomaterials is challenging,

The current study used a naturally derived assembly containing components of the plant virus tobacco mosaic virus (TMV) to overcome issues associated with synthetic systems. TMV was bioconjugated with a valine-citrulline monomethyl auristatin E (vcMMAE) pro-drug used in treating NHL. The resulting TMV-vcMMAE complex entered NHL cancer cells, where it was cleaved to release the active drug and killed the cancer cells. Dr. Steinmetz said, "Each platform technology offers unique advantages for drug delivery; plant virus–based nanotechnologies can be manufactured in high yields through molecular farming in plants, the protein-based materials are stable in biological media, and the biocompatible nanoscale scaffold offers an unparalleled opportunity for engineering allowing the introduction of various medical cargo. While still early in their development stages, plant virus–based drug delivery systems offer an intriguing platform technology for next-generation drug delivery."

Dr. Steven R. Goodman, editor-in-chief of *Experimental Biology and Medicine*, said, "Steinmetz and colleagues have utilized the plant virus TMV as a platform for delivering a valine-citrulline monomethyl auristatin E (vcMMAE) pro-drug into an *in vitro* model of human B-cell NHL. They observed cell uptake, endolysosomal location and possible cleavage of the prodrug, and cell killing. These studies provide the impetus for further testing of this plant virus drug delivery system for cancer treatment."

New Quad Pack from EpiCeram® Delivers 400 g of Itch Relief

PRNewswire: August 15, 2017 – PISCATAWAY, NJ, U.S.A. – PuraCap® Pharmaceutical today introduced the EpiCeram® controlled release skin barrier emulsion quad pack, which contains 400 g of eczema relief. EpiCeram® is an FDA-approved topical prescription emollient used to treat dry skin conditions and manage atopic dermatitis (AD).

As many as 10% of adults and children in the United States have eczema, making it one of the most common skin conditions. The new EpiCeram® quad pack contains four convenient 100 g airless pumps, making it ideal for patients who need to treat large skin areas or who require frequent application. The EpiCeram® quad pack can mean fewer trips to the pharmacy and a better value for patients with chronic AD.

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EpiCeram® controlled release skin barrier emulsion can help restore skin to its natural healthy condition while empowering eczema sufferers to finally feel comfortable in their own skin. The FDA-approved emollient contains all of the essentials for total skin barrier repair to help relieve itching, dryness, and redness. These include three essential lipids (ceramides, free fatty acids, and cholesterol) in a physiologically balanced ratio, which mimics the lipid concentration found in the skin. Formulated to help keep the skin at a healthy pH of 5, EpiCeram® works to repair the skin's barrier to help keep soothing moisture in and potential irritants out.

The 100 g airless pumps found in the quad pack answer the need for easily portable, evenly dispensed comfort for itchy skin.

With a unique controlled-release technology, EpiCeram® delivers 24 hour barrier repair benefits with just twice-daily application. EpiCeram® is also available in a 90 g tube and 225 g airless pump.

EpiCeram® is only available by prescription. Please consult your physician to find out how it can help manage your eczema. To obtain a valuable coupon to bring to your pharmacist, visit epiceram-us.com/coupon-offer. For more information or full prescribing information, go to www.epiceram-us.com.

PuraCap Pharmaceutical LLC is an emerging, fully integrated pharmaceutical company with expertise in product development, manufacturing, and distribution, bringing high-quality products and services to their customers. PuraCap's corporate structure supports a two-pronged approach for global growth in the areas of prescription brands and OTC and private label brands (PuraCap Pharmaceutical LLC) as well as prescription generics (PuraCap Laboratories LLC). Go to www.puracap.net for more information.

PAVmed Reports Second Quarter 2017 Financial Results

Business Wire: August 14, 2017 – NEW YORK, NY, U.S.A. – PAVmed Inc. (Nasdaq: PAVM, PAVMW), a highly differentiated, multiproduct medical device company, today announced financial results for the three and six months ended June 30, 2017, and provided a business update.

"During this past quarter and in recent weeks PAVmed has continued to grow stronger as a company, moving steadily towards major developmental, regulatory, and commercialization milestones, while exploring all opportunities to enhance shareholder value," said Lishan Aklog, M.D., PAVmed's chairman and chief executive officer.

"We significantly strengthened our balance sheet, raising $5.5 million in gross proceeds from seasoned and well-known healthcare investors," Dr. Aklog noted. "These funds provide us with sufficient capital to reach our key milestones well into 2018."

"Our development and commercialization strategy has been to focus our resources on three products in our pipeline with the greatest and nearest-term commercial opportunities—PortIO™, CarpX™, and DisappEAR™," Dr. Aklog stated.

PortIO is PAVmed's implantable intraosseous vascular access device, which is designed to provide short- or long-term access to the bone marrow cavity for the delivery of medications, fluids, or other substances, eliminating many of the shortcomings of existing devices, especially in patients with poor veins. "PortIO was submitted to the U.S. Food and Drug Administration (FDA) for 510(k) clearance for short-term use, and we continue to work with the FDA to demonstrate substantial equivalence to our selected predicate, with the *de novo* 510(k) pathway available to us as an alternative," said Brian deGuzman, M.D., PAVmed's chief medical officer. CarpX is PAVmed's percutaneous device to treat carpal tunnel syndrome, which is designed to eliminate the need for invasive carpal surgery, performed in 600,000 patients annually, resulting in decreased costs, reduced pain, accelerated recovery, and a lower the threshold for intervention. "CarpX is undergoing verification and validation testing, and we are on schedule for FDA 510(k) submission by the end of this quarter," Dr. deGuzman added. DisappEAR is PAVmed's reabsorbable, antibiotic-eluting pediatric ear tube device, which is designed to eliminate many of the shortcomings of currently available plastic ear tubes inserted in over one million children annually. The device utilizes a propriety aqueous silk technology licensed from Tufts University. "DisappEAR's development is progressing well and on schedule as we target FDA submission in 2018," Dr. deGuzman noted.

"These are exciting times for PAVmed," Dr. Aklog concluded. "Our recent financings have put us in a sound capital position, our lead products are advancing towards important milestones, and we remain nimble, creative, and resourceful as opportunities to enhance shareholder value present themselves. We greatly appreciate the strong commitment of our long-term shareholders and remain laser-focused on enhancing the value of the company for the benefit of all of our shareholders."

PAVmed Inc. is a highly differentiated, multiproduct medical device company employing a unique business model designed to advance products from concept to commercialization much more rapidly and with significantly less capital than the typical medical device

continued

company. This proprietary model enables PAVmed to pursue an expanding pipeline strategy with a view to enhancing and accelerating value creation. PAVmed's diversified pipeline of products address unmet clinical needs, have attractive regulatory pathways, and market opportunities and encompass a broad spectrum of clinical areas including carpal tunnel syndrome (CarpX™), medical infusions (NextFlo™ and NextCath™), interventional radiology (PortIO™ and NextCath™), tissue ablation and cardiovascular intervention (Caldus™), and pediatric ear infections (DisappEAR™). The company intends to further expand its pipeline through engagements with clinician innovators and leading academic medical centers. For further information, please visit www.pavmed.com.

Teva Announces FDA Approval of QVAR® RediHaler™ (Beclomethasone Dipropionate HFA) Inhalation Aerosol

Business Wire: August 7, 2017 – JERUSALEM, Israel – Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA) announced today that the U.S. Food and Drug Administration (FDA) has approved QVAR® RediHaler™ (beclomethasone dipropionate HFA) inhalation aerosol, a breath-actuated inhaler for the maintenance treatment of asthma as a prophylactic therapy in patients four years of age and older. QVAR® RediHaler™ is not indicated for the relief of acute bronchospasm. The product is expected to become commercially available in both 40 and 80 mcg strengths to patients by prescription during the first quarter of 2018.

QVAR® RediHaler™ differs from conventional metered-dose inhalers (MDIs) as it delivers medication via a breath-actuated MDI, eliminating the need for hand-breath coordination during inhalation. QVAR® RediHaler™ administers the same active drug ingredient found in QVAR® (beclomethasone dipropionate HFA) inhalation aerosol, with a different mode of delivery. In addition, QVAR® RediHaler™ is designed to be used without shaking or priming. It should not be used with a spacer or volume holding chamber.

"When working to manage asthma on a daily basis, proper administration of medication is of paramount importance," said Dr. Warner W. Carr, M.D., associate medical director of Southern California Research at Allergy and Asthma Associates of Southern California Medical Group in Mission Viejo, California. "However, research has indicated that approximately 76% of patients still struggle to use their MDI inhalers correctly, thus placing them at increased risk for asthma exacerbations. From a clinical perspective, QVAR® RediHaler™ is a much-needed treatment option for these patients who may be experiencing continued difficulty with hand-breath coordination."

"It's important that we uncover new opportunities to take longstanding, clinically effective medications, such as QVAR®, and incorporate them into device technologies that may help address key ongoing issues for patients, including inhaler technique," said Tushar Shah, M.D., head, late stage development at Teva Pharmaceuticals. "The FDA approval of QVAR® RediHaler™ brings to market inhaler technology aimed at enabling patients to more accurately administer the medication and ensuring they are receiving a proper dose with each inhalation."

QVAR® MDI with dose counter, the currently available form of QVAR®, was originally approved by the FDA in 2014. Teva plans to discontinue sales of this current QVAR® MDI formulation upon the launch of QVAR® RediHaler™ in the first quarter of 2018. Patients and caregivers are encouraged to speak with a healthcare professional about how this transition may impact their current treatment plan.

This approval is supported by Teva's clinical development program for QVAR® RediHaler™, which includes data from one phase I and four phase III studies that evaluated the safety and efficacy of the product in asthma patients ages four years and older.

July

Perrigo Announces the Launch of the AB Rated Generic Version of Transderm Scop® 1.5 mg

PRNewswire: July 31, 2017 – DUBLIN, Ireland – Perrigo Company plc (NYSE; TASE: PRGO) and its co-development partner Aveva Drug Delivery Systems, Inc., an Apotex Company, today announced the prescription pharmaceutical launch of scopolamine 1.5 mg transdermal system patch, the AB rated generic equivalent to Transderm Scop® (scopolamine 1.5 mg).

Transderm Scop® (scopolamine 1.5 mg) transdermal system patch is an anticholinergic indicated for the prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia after surgery in adults. Annual market sales for the 12 months ending May 2017 were approximately $158 million.

Perrigo executive vice president and president Rx pharmaceuticals John Wesolowski stated, "I would like to thank the R&D and regulatory teams for their efforts to bring this difficult-to-manufacture product to market. This launch is another example of our ability to deliver complex generic products to patients at more affordable prices."

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Perrigo Company plc, a leading global healthcare company, delivers value to its customers and consumers by providing Quality Affordable Healthcare Products®. Founded in 1887 as a packager of home remedies, Perrigo has built a unique business model that is best described as the convergence of a fast-moving consumer goods company, a high-quality pharmaceutical manufacturing organization, and a world-class supply chain network. Perrigo is the world's largest manufacturer of over-the-counter (OTC) healthcare products and supplier of infant formulas for the store-brand market. The company also is a leading provider of branded OTC products throughout Europe and the United States, as well as a leading producer of "extended topical" prescription drugs. Perrigo, headquartered in Ireland, sells its products primarily in North America and Europe, as well as in other markets, including Australia, Israel, and China. Visit Perrigo online at www.perrigo.com.

Aradigm Submits New Drug Application (NDA) to FDA for U.S. Marketing Approval of Linhaliq in Non-Cystic Fibrosis Bronchiectasis

Business Wire: July 27, 2017 – HAYWARD, CA, U.S.A. – Aradigm Corporation (NASDAQ: ARDM) (the "company") today announced it has submitted its New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for Linhaliq™ for the treatment of non-cystic fibrosis bronchiectasis (NCFBE) patients with chronic lung infections with *Pseudomonas aeruginosa* (*P. aeruginosa*).

Pursuant to the Food and Drug Administration Modernization Act of 1997 (FDAMA) Sec. 115(a) and FDA guidance, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998), Aradigm is submitting the Linhaliq NDA based on the positive phase 3 pivotal clinical trial ARD-3150-1202 (ORBIT-4) and confirmatory evidence from phase 3 study ARD-3150-1201 (ORBIT-3) and phase 2b study ARD-3150-0902 (ORBIT-2), together with other supporting evidence from proprietary preclinical and clinical studies, as well as referencing other information about ciprofloxacin from publicly available sources.

Aradigm received orphan drug designation for liposomal ciprofloxacin for inhalation for the management of bronchiectasis and of Linhaliq for the management of bronchiectasis. Additionally, for Linhaliq, Aradigm was granted qualified infectious disease product (QIDP) designation for the treatment of NCFBE patients with chronic lung infections with *P. aeruginosa* followed by fast track designation.

The FDA has a 60-day filing review period to determine whether the NDA is complete and acceptable for filing.

Linhaliq, formerly known as Pulmaquin®, is composed of a mixture of liposome encapsulated and unencapsulated ciprofloxacin. Ciprofloxacin, available in oral and intravenous formulations, is a widely prescribed antibiotic. It is used often to treat acute lung infections because of its broad-spectrum antibacterial activity against various bacteria, such as *P. aeruginosa*. There are currently no treatments approved for NCFBE patients to prevent and reduce the number of pulmonary exacerbations (PEs).

Linhaliq was evaluated in two phase 3 studies (ORBIT-3 and ORBIT-4) to determine its safety and effectiveness as a once-a-day inhaled formulation for the chronic treatment of patients with NCFBE who have chronic lung infections with *P. aeruginosa*.

The phase 3 clinical program for Linhaliq in NCFBE consisted of two worldwide, double-blind, placebo-controlled pivotal trials (ORBIT-3 and ORBIT-4) that were identical in design except for a pharmacokinetics substudy that was conducted in one of the trials. Each trial enrolled NCFBE patients (278 in ORBIT-3 and 304 in ORBIT-4) into a 48-week double-blind period consisting of six cycles of 28 days on treatment with Linhaliq or placebo plus 28 days off treatment, followed by a 28 day open label extension in which all participants received Linhaliq (total treatment duration, including the double-blind period, of approximately one year). The superiority of Linhaliq versus placebo during the double-blind period was evaluated in terms of the primary endpoint—time to first PE—while key secondary endpoints included the reduction in the number of PEs and the number of severe PEs, and improvements in quality of life measures. Lung function was monitored as a safety indicator.

Aradigm discussed the results of the phase 3 studies at meetings with FDA in December 2016 and March 2017. Based on these discussions, the statistical analysis of the results was changed from the prespecified plan to stratification based on sex and the frequency of pulmonary exacerbations in the prior year, as the stratum for current smokers contained a small number of subjects.

Top-line results for the two phase 3 studies using the new stratification are described below.

In ORBIT-4 the median time to first PE was 230 days in the Linhaliq treatment group as compared to 158 days in the placebo group. This increase of 72 days in the median time to first PE was statistically significant ($P = 0.0323$) using stratified unweighted log-rank analysis. For the first secondary efficacy endpoint, there was a 37% reduction in the frequency of PEs over the 48-week treatment

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period in the Linhaliq treatment group as compared to the placebo group. This result was statistically significant ($P = 0.0006$). In the analysis of the second secondary endpoint, a statistically significant 60% reduction in the frequency of severe PEs in the Linhaliq group compared with placebo was found ($P = 0.0031$).

In ORBIT-3 the median time to first PE was 214 days in the Linhaliq treatment group as compared to 136 days in the placebo group. This increase of 78 days in the median time to first PE was similar to ORBIT-4 but was not statistically significant ($P = 0.9743$). For the first secondary efficacy endpoint, there was a 15% reduction in the frequency of PEs over the 48-week treatment period in the Linhaliq treatment group as compared to the placebo group, but it was not statistically significant ($P = 0.2565$). In the analysis of the second secondary endpoint, a statistically nonsignificant 20% reduction in the frequency of severe PEs in the Linhaliq group compared with placebo was found ($P = 0.4827$).

In neither trial did Linhaliq compared to placebo demonstrate a statistically significant improvement in the third secondary endpoint of the quality of life using the difference in the respiratory domain score of the QoL-B questionnaire between baseline and week 48.

Both studies demonstrated a statistically significant reduction in *P. aeruginosa* density at day 28, the end of the first on-treatment period (ORBIT-3: $P < 0.0001$; ORBIT-4: $P < 0.0001$). For each study, the magnitude of this antibiotic effect remained persistent throughout all on-treatment periods. Similarly, the phase 2b trial ORBIT-2 met its primary efficacy endpoint of reduction of *P. aeruginosa* density at day 28 ($P = 0.002$).

Linhaliq was generally safe and well tolerated in both phase 3 studies. There were no significant differences in the changes of lung function (FEV1 % predicted and FVC % predicted) or symptoms of airway irritation between the Linhaliq and placebo groups in the two studies. Overall, the incidence of all treatment emergent adverse events (TEAE) was similar between the Linhaliq and placebo groups in both ORBIT-3 (Linhaliq: 89.6%; placebo: 91.6%) and ORBIT-4 (Linhaliq: 86.9%; placebo: 96.9%). In ORBIT-3 the rates of serious TEAEs were 30.6% with Linhaliq and 25.3% with placebo, while in ORBIT-4 the rates were 17.0% versus 28.6%.

For each phase 3 study, the randomization rate of Linhaliq-treated subjects to placebo was 2 to 1. There were 8 deaths in ORBIT-3 (Linhaliq: 5 [2.7%]; placebo: 3 [3.2%]) and 6 deaths in ORBIT-4 (Linhaliq: 2 [1.0%]; placebo: 4 [4.1%]). None of the deaths was considered related to Linhaliq or placebo by the investigators. The most frequently observed treatment-related TEAEs were of respiratory/thoracic/mediastinal nature and were reported in ORBIT-3 by 25.7% of subjects with Linhaliq and in 21.1% of subjects with placebo, while the rates in ORBIT-4 were 16.5% with Linhaliq versus 20.4% with placebo. There were no deaths in ORBIT-2.

After the completion of the 48-week double-blind period of the phase 3 studies, both Linhaliq and placebo treated patients were given the opportunity to receive Linhaliq in a 28-day open label extension period. Eighty-nine percent of the patients who completed ORBIT-3 and 91% percent of the patients who completed ORBIT-4 enrolled in the extension period.

Further information about the analyses of the phase 3 results is presented at Aradigm's website www.aradigm.com. In addition, Aradigm intends to submit Linhaliq for marketing authorization in the European Union for the treatment of patients with NCFBE who have chronic lung infections with *P. aeruginosa*.

Aradigm is an emerging specialty pharmaceutical company focused on the development and commercialization of drugs for the prevention and treatment of severe respiratory diseases. Aradigm has completed phase 3 development of Linhaliq (an investigational proprietary formulation of ciprofloxacin for inhalation) for the treatment of NCFBE. Aradigm's inhaled ciprofloxacin formulations including Linhaliq are also product candidates for treatment of patients with cystic fibrosis and non-tuberculous mycobacteria, and for the prevention and treatment of high-threat and bioterrorism infections, such as inhaled tularemia, pneumonic plague, melioidosis, Q fever, and inhaled anthrax. More information about Aradigm can be found at www.aradigm.com. Aradigm, Pulmaquin, and the Aradigm logo are registered trademarks of Aradigm Corporation. Linhaliq is a registered trademark of Grifols, S.A.

Ophthotech Expands Focus with Development for Ophthalmic Orphan Diseases

Business Wire: July 26, 2017 – NEW YORK, NY, U.S.A. – Ophthotech Corporation (Nasdaq: OPHT) today announced that the company is pursuing a strategy to leverage its clinical experience and retina expertise to identify and develop therapies to treat multiple orphan ophthalmic diseases for which there are limited or no treatment options available. In parallel, the company continues its ongoing age-related retinal programs and its business development efforts to obtain rights to additional products, product candidates, and technologies to treat ophthalmic diseases, particularly those of the back of the eye.

- Ophthotech's orphan ophthalmic disease strategy will be led by a randomized, controlled clinical trial assessing the efficacy and safety of Zimura® (avacincaptad pegol), the company's C5 complement inhibitor, for Stargardt disease, a devastating inherited

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retinal orphan disease causing vision loss during childhood or adolescence for which patients have no approved treatment. This trial is scheduled to start by the end of this year.

- The company is continuing its programs in age-related eye diseases, including the planned initiation of a phase 2a clinical trial of Zimura® in combination with anti-VEGF therapy for wet age-related macular degeneration (AMD) and a phase 2a clinical trial of Zimura® in combination with anti-VEGF therapy for idiopathic polypoidal choroidal vasculopathy. Both of these trials are scheduled to start by the end of this year.

- The company's phase 2/3 clinical trial of Zimura® as a monotherapy for the treatment of geographic atrophy, a form of dry AMD, is ongoing. The company has maintained a limited number of trial sites for this study and will reassess its strategy for this study following results of a competitor's complement trial for geographic atrophy, which are expected by year end.

- The National Eye Institute is leading a phase 1/2 clinical trial of the company's drug candidate, Fovista® (pegpleranib) in combination with anti-VEGF therapy for the treatment of retinal manifestations of the orphan disease Von Hippel-Lindau Syndrome.

- Ophthotech is also planning a phase 2a clinical trial of Zimura® for intermediate/posterior noninfectious uveitis, a rare inflammatory disease of the back of the eye, and a potential preclinical program with Fovista® for retinoblastoma, a rare cancer of the eye in children. These studies are planned to start in 2018.

"We are excited to move the company forward with a goal of becoming a leader in the development and commercialization of ophthalmic therapeutics for orphan diseases and for larger indications in the back of the eye, such as age-related retinal diseases," stated Glenn P. Sblendorio, chief executive officer and president of Ophthotech. "We believe that we will be well positioned as a company with multiple shots on goal to bring ophthalmic therapeutics to market. We are also continuing our business development efforts with the goal of broadening and advancing our pipeline. We are committed to developing treatments for patients with devastating ophthalmic diseases and to maximizing value for our shareholders."

Supporting the company's strategy for the development of Zimura® in Stargardt disease is a recently published independent, peer-reviewed paper in the prestigious journal *Proceedings of National Academy of Science* (*PNAS*) from a world-class laboratory at the University of California, Los Angeles (UCLA) that highlights the potential role of complement inhibition in addressing the urgent unmet medical need in Stargardt disease. Additionally, independent literature also supports the scientific evidence for the potential role of complement and specifically the membrane attack complex (MAC) in this disease. The clinical safety data for Zimura® from the company's completed early stage age-related macular degeneration trials provide a basis to proceed directly to a randomized, controlled clinical trial to assess the safety and efficacy of Zimura® in Stargardt disease.

The company also announced that it has entered into an agreement with the Foundation Fighting Blindness (FFB). FFB is a highly distinguished organization recognized for its scientific commitment to orphan inherited retinal degenerative diseases with an established network of scientists and a robust patient registry. Ophthotech has engaged FFB to provide the company with information from its publicly available ProgStar study, the largest natural history study on Stargardt disease to date, which Ophthotech plans to use in the design of its planned clinical trial of Zimura® for Stargardt disease, and to potentially assist with the company's other orphan degenerative retinal programs.

"We commend Ophthotech for recognizing the underserved patients afflicted with Stargardt disease for whom currently there is no available FDA-approved treatment option," stated Patricia Zilliox, Ph.D., FFB's Clinical Research Institute chief drug development officer. "We are delighted and honored to team up with Ophthotech, thereby complementing their expertise in ophthalmic drug development with our experience in studying Stargardt disease."

"We are fortunate to have the opportunity to work closely with the Foundation Fighting Blindness," stated Kourous A. Rezaei, M.D., senior vice president of medical strategy. "We also intend to work closely with the FDA over the next few months to discuss the regulatory pathway for our Zimura® Stargardt program."

The company also announced changes to its wet AMD program for Zimura®. The company believes that supplementing anti-VEGF therapy with an anti-complement such as Zimura® in wet AMD may have the potential to further enhance the efficacy of anti-VEGF monotherapy and decrease unwanted side effects in wet AMD from anti-VEGF drugs. A recent peer-reviewed publication from the *Journal of Clinical Investigation* from the prestigious Scripps Research Institute citing the role of anti-VEGF therapy in complement activation supports this thesis. Due to a new study design and updated enrollment criteria, the company will cease enrollment in its current phase 2a clinical trial of Zimura® in wet AMD, and initiate a new phase 2a clinical trial to assess whether it can replicate

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findings from its previous phase 1/2a clinical trial. The company will be assessing a range of dosing regimens before committing to a larger and more costly trial. This trial is scheduled to initiate before the end of the year.

"The opportunities to develop orphan drugs for ophthalmic diseases along with some intriguing new developments regarding the role of complement in anti-VEGF therapy allow us to focus our resources and efforts on science-driven solutions in addressing the unmet need in ophthalmic diseases," stated Mr. Sblendorio. "In addition, we have reviewed a large number of assets and technology platforms over the past few months and are actively continuing to review, in a prudent manner, assets or technology platforms which would fit into our strategic goals in addition to other compelling ophthalmology opportunities." Ophthotech is a biopharmaceutical company specializing in the development of novel therapeutics for diseases of the eye. For more information, please visit www.ophthotech.com.

New Workflow Is First End-to-End Solution for Extrusion-Based Drug Implant Production

PRNewswire: July 26, 2017 – KARLSRUHE, Germany – To meet growing demand for innovative drug delivery systems in the pharmaceutical industry, drug formulation scientists can now use the first commercially available, fully integrated solution for polymer-based drug implant development and production using hot melt extrusion (HME). This new drug development workflow provides pharmaceutical manufacturers with a complete end-to-end manufacturing line from a single supplier.

The Thermo Scientific Pharma mini implant line is built around the Thermo Scientific Pharma mini HME twin-screw micro compounder. It provides drug developers, process manufacturing scientists, and engineers with a continuous and fast production process designed to improve product quality, maximize operator safety, and reduce the risk of contamination. This integrated production line is also designed to allow contract research and manufacturing organizations (CRO/CMO) to develop and optimize small-scale formulations before engaging in larger-scale production.

"With a single subcutaneous injection, advanced drug implants can release a therapeutic substance that can provide patients with improved drug compliance, effective disease treatment, or controlled hormonal regulation for weeks or even months," said Hanna Granö-Fabritius, senior business director, material characterization for Thermo Fisher Scientific. "Pharmaceutical manufacturers are seeking fast, reliable solutions for continuous production of novel drug delivery systems. Our new, automated implant line offers a hot melt extrusion solution designed to minimize formulation development time."

The Thermo Scientific Pharma mini implant line incorporates a range of components in an innovative configuration. In addition to the Pharma mini HME micro compounder, components include:

- A containment valve to add the active pharmaceutical ingredient (API) and the polymer, designed to protect the operator from exposure to the API and preventing contamination of the API;
- A gravimetric feeder to deliver the API/polymer into the micro compounder for heating and mixing before the melt is extruded through a die that creates a continuous filament;
- New bi-axial lasers that measure the thickness or diameter of the filament to adjust the stretching or "take-off" speed of the conveyor belt; and
- Proprietary equipment that cuts the filament to a desired implant length while maintaining "roundness" without deforming the implant shape.

For more information on the Thermo Scientific Pharma mini implant line, please visit www.thermofisher.com/implantline.

AzarGen Biotechnologies Granted European Patent for Plant-Made Production of Recombinant Human Surfactant Protein-B

PRNewswire: July 25, 2017 – STELLENBOSCH, South Africa – AzarGen Biotechnologies (Pty) Ltd. (Stellenbosch, South Africa) announced that it has received grant status for the patent application Production of Human Pulmonary Surfactant Protein-B in Plants (EP3013963) from the European Patent Office.

Exogenous pulmonary surfactant is routinely being used in surfactant replacement therapy applications to treat neonatal respiratory distress syndrome (nRDS). Animal-derived surfactant contains very low amounts of surfactant protein-B (SP-B), one of the key proteins that, combined with phospholipids, are essential to lower surface tension and increase lung compliance during breathing.

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"With the focus on developing a new surfactant preparation, we believe that by combining a high concentration of functional recombinant human SP-B and analogs thereof with a synthetic lipid mixture we may significantly improve pulmonary surfactant dynamics with potential use in various inhalation drug delivery platforms," said Dr. Cobus Zwiegelaar, COO of AzarGen. "Using proprietary technology by iBio, Inc. (NYSE MKT: IBIO), a leader in developing plant-based biopharmaceuticals, the plant-made production platform offers new hope to produce recombinant human SP-B proteins in sufficient amounts and purity, at a significantly lower cost."

The biological complexity of native human SP-B structure presents a major obstacle to obtain significant amounts of active/functional SP-B and different methodologies ranging from the extraction from animal (bovine or porcine) minced lungs to solid-phase synthetic peptide synthesis may be expensive and labor intensive.

"We are optimistic about the commercial and public health benefits of combining the inventive work of AzarGen with iBio's proprietary technologies and capabilities," said Robert Erwin, president of iBio. "We are committed to working closely with AzarGen to reduce the time usually required with traditional technologies to move product development and testing from one stage to the next, for both good business reasons and to provide the best possible outcome for patients."

AzarGen aims to develop novel synthetic pulmonary surfactant formulations comprising functional recombinant human SP-B and/or analogs thereof. This could extend the application of an exogenous surfactant, used alone for surfactant replacement therapy or in combination with other therapeutics, to treat a wider range of respiratory conditions."

iBio, a leader in developing plant-based biopharmaceuticals, provides a range of product and process development, analytical, and manufacturing services at the large-scale development and manufacturing facility of its subsidiary iBio CMO LLC in Bryan, Texas. The facility houses laboratory and pilot-scale operations, as well as large-scale automated hydroponic systems capable of growing over four million plants as "in process inventory" and delivering over 300 kilograms of therapeutic protein pharmaceutical active ingredient per year. Facility capacity can be doubled by adding additional plant growth equipment in a space already reserved for that purpose.

iBio applies its technology for the benefit of its clients and the advancement of its own product interests. The company's pipeline is comprised of proprietary candidates for the treatment of a range of fibrotic diseases including idiopathic pulmonary fibrosis, systemic sclerosis, and scleroderma. IBIO-CFB03, based on the company's proprietary gene expression technology, is the company's lead therapeutic candidate being advanced for IND development. Further information is available at www.ibioinc.com.

AzarGen is a biotechnology company focused on developing human therapeutic proteins using advanced genetic engineering and synthetic biology techniques in plants. The company's lead therapeutic candidate is a recombinant human surfactant protein (based on rh-SPB) targeted for various respiratory disease conditions. AzarGen has developed proprietary synthetic DNA promoters for various expression platform applications in plant-made pharmaceuticals, synthetic biology, and GMO-crop improvement.

The AzarGen management team is supported by an experienced advisory board for strategic guidance and intellectual property management. Based in Stellenbosch, South Africa, AzarGen has made great progress to move a portfolio of proprietary biopharmaceutical products forward with support from South Africa's Industrial Development Corporation (IDC).

Teva Announces the Launch of Generic Vagifem® in the United States

Business Wire: July 24, 2017 – JERUSALEM, Israel – Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA) today announced the launch of a generic version of Vagifem®1 (estradiol vaginal inserts), 10 mcg in the United States. Estradiol vaginal inserts are an estrogen indicated for the treatment of atrophic vaginitis due to menopause.

Estradiol vaginal inserts add to Teva's existing portfolio of more than 70 women's health products. With nearly 600 generic medicines available, Teva has the largest portfolio of FDA-approved generic products on the market and holds the leading position in first-to-file opportunities, with over 100 pending first-to-files in the United States. Currently, one in six generic prescriptions dispensed in the United States is filled with a Teva generic product.

"Our expanding portfolio of oral contraceptives and hormone replacement therapies gives women a broader choice of products to manage their health needs cost-effectively," said Andy Boyer, CEO and president, global generic medicines, North America, at Teva. "With this addition, patients and healthcare providers who prefer this unique dosage-form now have another, more affordable option for treatment."

Estradiol vaginal inserts had annual sales of approximately $379 million in the United States according to IMS data as of May 2017. ■