CRS Leading Delivery Science and Technology

Newsletter

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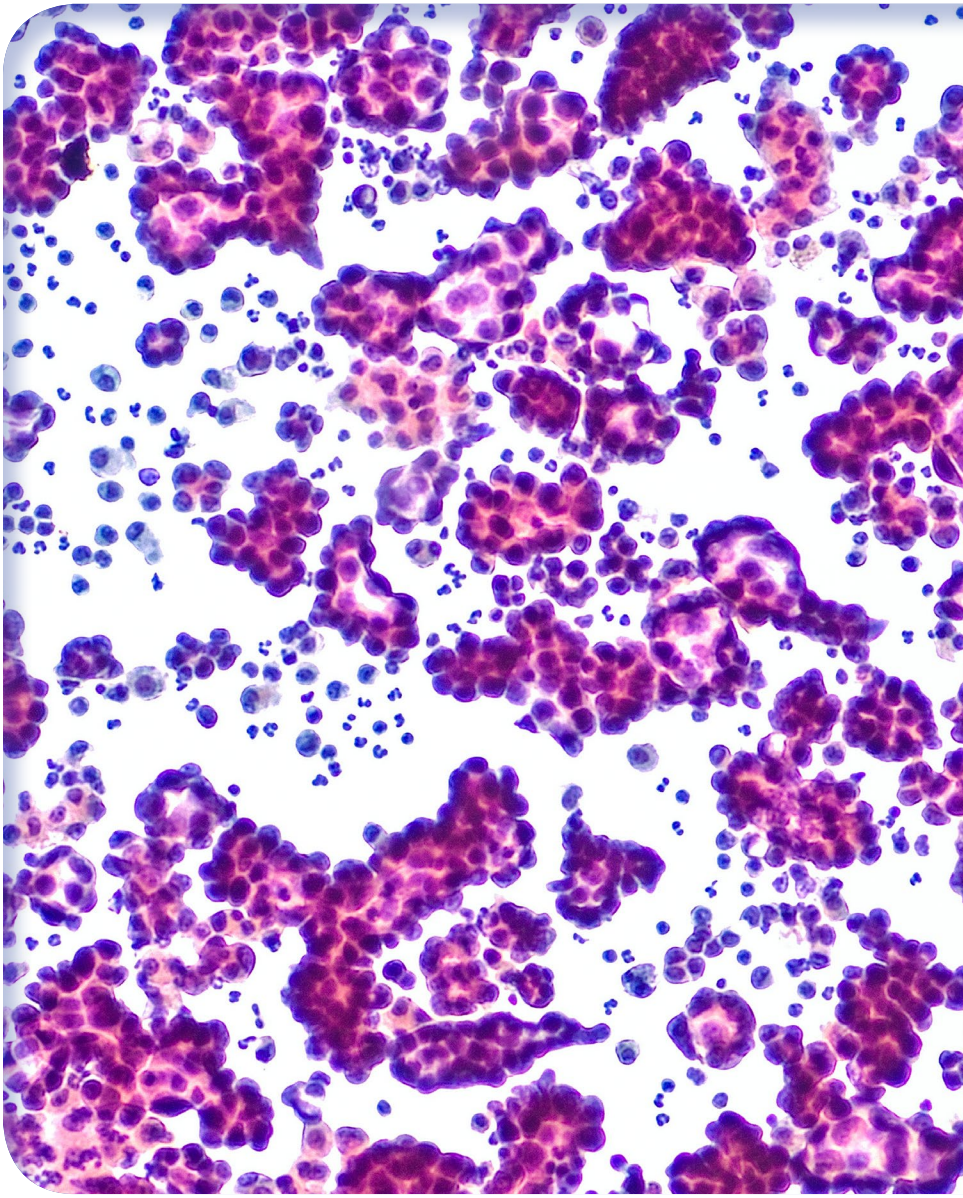
What's Inside



Science. **People.** *Products.*

Connect and collaborate with delivery science and technology leaders from academia and industry, under one roof at **#CRSboston**

Join us in **Boston, Massachusetts, U.S.A.** from **July 16–19** for the **2017 Controlled Release Society Annual Meeting & Exposition**.

Registration is now open!
Visit **controlledreleasesociety.org/CRSboston** for details.

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Cover image: Malignant effusion: Pleural fluid cytology of lung (pulmonary) papillary adenocarcinoma, a type of non small cell carcinoma. Pap stain. David Litman / Shutterstock.com

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

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

Please Come to Boston

It's springtime in the northern hemisphere, with the days getting longer and warmer, and the flowers blooming. Even though I now live in Texas, I'm reminded of my many walks around Boston and Cambridge in the spring. I lived in the Boston area for twenty years and developed a tradition of taking a day, in May, to enjoy the city and spring.

In the morning, I would grab a coffee and a croissant at Kendall Square and sit on one of the benches along Memorial Drive, overlooking the Charles River, and enjoy the view. I would then walk across the Longfellow Bridge, stopping along the way to see the sailboats or duck boat. After that, I would walk down the Esplanade, cross over Storrow Drive, and walk through Back Bay. After a late lunch, I would continue, through the Public Garden and across the Boston Common. Next was a trip on the T from the Park St. station to the Hynes Convention Center station. Once on Massachusetts Ave., I then crossed the Massachusetts Ave. Bridge and walked through MIT, to end up back at Kendall Square. By that time, the sun was setting and it was time to go home. I have many fond memories of Boston, my annual walks, and all the people I met while living in Massachusetts.

This year's CRS annual meeting is in Boston. Boston is now a hub for biotechnology and medical devices, growing since the 1980s. Cambridge and Kendall Square are home to several large pharma and biotech companies, Harvard, and MIT, as well as start-ups and the Massachusetts Biotechnology Council. Boston is home to the Massachusetts Medical Device Industry Council (MassMEDIC).

The annual meeting will feature prominent scientists discussing the future of delivery science, emerging technologies, and our industry's current and future challenges. Plenary speakers include Prof. Robert Langer (MIT), Dr. Henry Brem (Johns Hopkins University), Dr. Amar Sawhney (Ocular Therapeutix), and Prof. Paula Hammond (MIT). Premeeting workshops will cover novel delivery platforms, basic concepts of oral drug delivery, and enabling successful liposomal formulation. Thirteen scientific sessions will offer an exciting lineup of invited speakers and moderated discussions. Include the poster sessions, technology forums, networking events, and receptions, and you have all the activities for a wonderful time in Boston.

Inside this issue of the *CRS Newsletter*, you will find two Scientifically Speaking articles, more details about the annual meeting, the *DDTR* Update, and Companies/People in the News.

Hopefully you will be able to attend the Boston meeting this July, see an old friend or make a new one, and take a walk. If not, then maybe set aside a day of your own, to walk and enjoy your favorite park, beach, mountain, or city.

All the best,
Steven Giannos ■

Annual Meeting Program Highlights

Be inspired by the best and brightest in delivery science at the Controlled Release Society Annual Meeting & Exposition in Boston, Massachusetts, U.S.A. Attend to hear prominent scientists discuss the future of delivery science, learn about emerging technologies to solve our industry's challenges, and participate in discussions relevant to the delivery science and technology area.

Get the most from the annual meeting with these highly focused premeeting educational workshops and scientific sessions!

Premeeting Workshops

Get more from the annual meeting with these highly focused premeeting workshops.*

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

Saturday, July 15 • 8:00 a.m. – 1:30 p.m.

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

What I wish I knew when I started many years ago and paid the price for not knowing
Saturday, July 15 • 9:00 a.m. – 5:00 p.m.

Enabling Successful Liposomal Formulation from Scratch – Lipid Synthesis, CMC, Regulatory, and Case Study

Sponsored by MilliporeSigma POLYMUN SCIENTIFIC

Sunday, July 16 • 8:00 a.m. – 1:00 p.m.

Attend an additional workshop sponsored by:

- Catalent

* *There is an additional fee and space is limited, so be sure to register early*!

Mini-Symposia

Take a detailed look into a specific interest within delivery science—expert speakers will share their research on the topic.

- Intracellular Delivery
- Natural Structures as Drug Carriers

Scientific Sessions

Choose from 13 Scientific Sessions offering an exciting lineup of invited speakers and moderated discussions.

Advances in Manufacture, Characterization, Stability, and Regulation

- Diane Burgess, University of Connecticut, U.S.A.
- Yue (Helen) Teng, U.S. Food & Drug Administration, U.S.A.

Biologically Active Excipients and Carriers

- Jean-Christophe Leroux, ETH Zurich, Switzerland

Cell Therapies

- Garry Duffy, Royal College of Surgeons in Ireland, Ireland
- Kristy Wood, Intellia Therapeutics Inc., U.S.A.

Delivery of Complex and Labile Molecules

- Ann Daugherty, Genentech Inc., U.S.A.
- Ana Jaklenec, Massachusetts Institute of Technology, U.S.A.

Delivery of Drug Combinations

- Glen Kwon, University of Wisconsin-Madison, U.S.A.
- Yi Yan Yang, Institute of Bioengineering and Nanotechnology, Singapore

Delivery Technologies in Nutraceuticals, Foods, and Oral Products

- Jingyuan Wen, University of Auckland, New Zealand
- Cuie Yan, PepsiCo R&D Global Beverage, U.S.A.

Encapsulation and Controlled Release for Industrial Applications

- Phil Santangelo, Georgia Tech, U.S.A.
- Chris Tucker, Dow Chemical, U.S.A.

continued

Improving *in Vitro* Methodologies, Predicting Outcomes
- Yvonne Perrie, University of Strathclyde, United Kingdom
- Christer Tannergren, AstraZeneca, Sweden

Medical Devices
- Young Bin Choy, Seoul National University, South Korea
- Carlo Giovanni, Brigham and Women's Hospital, Harvard Medical School, U.S.A.

Modeling and Simulation: Interplay of Animal and Human Pharmaceutical Development
- Marilyn Martinez, FDA Center for Veterinary Medicine, U.S.A. and Devendra Pade, Certara, U.S.A.
- Wen Lin, Novartis, U.S.A.

New Directions for Polymers in Drug Delivery
- Nicholas Peppas, University of Texas at Austin, U.S.A.
- Ashutosh Chilkoti, Duke University, U.S.A.

Ocular Drug Delivery
- Mikhail Ostrovsky, Institute of Biochemical Physics, Russian Academy of Science, Russia
- Eliana Souto, University of Coimbra, Portugal

Overcoming Biological Barriers in Drug Delivery
- Cristianne Rijcken, Cristal Therapeutics, The Netherlands
- Wouter Hinrichs, University of Groningen, The Netherlands

Pearls of Wisdom Session

This session will debate the merits of human tumor models with the ultimate goal of setting guidelines that drug delivery scientists could consider in protocols for evaluating candidate anticancer drugs.

Human Tumors in Rodents: A Valuable and Predictive Tool or a Waste of Time

Monday, July 17 • 4:15 p.m. – 5:15 p.m.

Poster Sessions

Gain inspiration for your own research as you meet with authors from around the world! Hundreds of poster presentations will be on display showcasing the latest research, developments, and innovations in our industry.

Technology Forums

Sunday, July 16 • 9:00 a.m. – 1:00 p.m.

Attend a small group forum to discover more about a company's newest research, product, or service. Check out the participating companies (as of March 17, 2017):

- Bluestar Silicones
- Cambridge Design Partnership
- DATA Detection Technologies
- Evonik Corporation
- Gattefossé
- Suven Life Sciences Limited
- Wyatt Technology Corporation

Industry Roundtables

Join your colleagues for these in-depth interactive sessions where a panel of experts will share their findings and opinions, creating an extended discussion on focused topics.

Running with Your Idea: How to Successfully Navigate Your Start-Up

Sponsored by Pfizer

Sunday, July 16 • 3:00 – 4:30 p.m.

Attend additional sessions sponsored by:

- Boehringer Ingelheim
- Capsugel
- Catalent
- Cambridge Design Partnership
- C&DP Division
- Patheon ■

Formulation and Delivery of Mono-*N*-Oxide Vinblastine Liposomal Formulation for Targeting Non-Small Cell Lung Cancer with Hypoxic Environments

Vidhi M. Shah, Duc X. Nguyen, Adel Al-Fatease, and Adam W. G. Alani
Department of Pharmaceutical Sciences, College of Pharmacy, Oregon State University, U.S.A.

Introduction

In non-small cell lung cancer (NSCLC), the level of oxygenation surrounding the cancerous cells is low compared with normal tissue owing to the rapid growth of the tumor cells. The decreased blood circulation results in development of pockets of lower oxygen levels, resulting in hypoxia.[1] This abnormality in the tumor microenvironment results in a unique condition not prevalent in normal tissues. A number of functional groups such as *N*-oxides, nitroaromatics, and quinones can be reduced by several endogenous reductive enzymes that are overexpressed in the hypoxic tumor tissues.[2] Forming a prodrug by incorporating these groups, which can undergo reduction to the active moiety in the hypoxic tissue, has been utilized recently as an approach for solid tumor targeting. Among the molecules developed is TH-302 a 2-nitroimidazole conjugated prodrug of bromo-isophosphoramide mustard, which is the only molecule that has progressed to the later stages of clinical development.[3] However, the molecule did not meet its primary endpoint of improving overall survival. Following the same strategy, Cascade Prodrug Inc. developed vinblastine–*N*-oxide (CPD100, U.S. patent 20120107230), an *N*-oxide prodrug for vinblastine (VBL). VBL is a common anticancer molecule and forms an important role in many chemotherapeutic regimens, but like any other antitumor agent, it has severe side effects associated with its use, such as peripheral neuropathy and nervous system toxicity.[4] The prodrug preferentially reduces at its nitrogen atom in cells or tissues by various endogenous reductases found only in hypoxic conditions, to the active moiety VBL, thus resulting in selective targeting (Figs. 1 and 2).

Preliminary data indicate that CPD100 has a plasma half-life ($t_{1/2}$) of 0.44 h and a maximum tolerated dose (MTD) of 40 mg/kg compared with VBL's plasma $t_{1/2}$ of 4.5 h and MTD of 5 mg/kg in mice. Thus, although the prodrug displays an excellent safety and toxicity profile compared with the parent compound, its potential use is limited by its unfavorable pharmacokinetic profile, specifically the short $t_{1/2}$. Thus, a drug delivery system is needed to increase the circulation half-life and efficacy of CPD100.

Liposomes are colloidal carriers that consist of an aqueous core enclosed by a concentric lipid bilayer vesicle capable of loading both hydrophilic and hydrophobic moieties. They usually range between 0.025 and 2.5 µm in diameter. A liposomal delivery system increases the efficacy of a drug by increasing the therapeutic concentration of the drug at the site of action and/or by decreasing the toxicity of the drug to normal tissues. The encapsulation of drugs in liposomes results in increasing the solubility and stability of drugs *in vivo* and has a major effect on the pharmacokinetics of drugs.[5] In this work, we have developed a sphingomyelin/cholesterol liposomal formulation of CPD100 (CPD100Li), and we assessed the safety, efficacy, and pharmacokinetic profiles in *in vitro* and *in vivo* models.

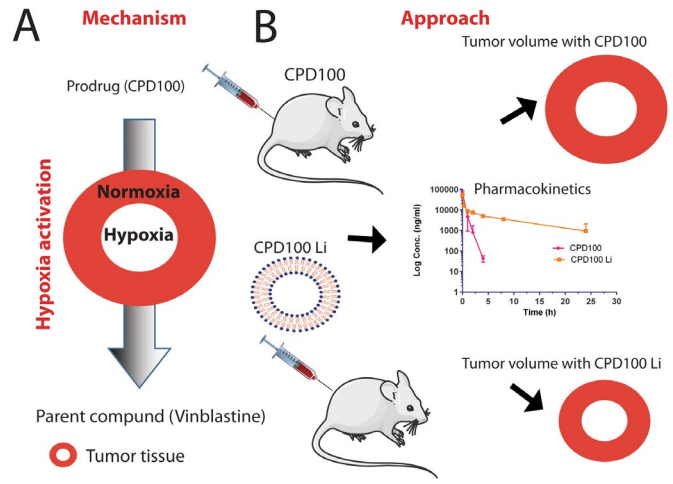

Figure 1. *Graphical abstract: (A) mechanism, and (B) approach. ©Elsevier; reproduced by permission.*[11]

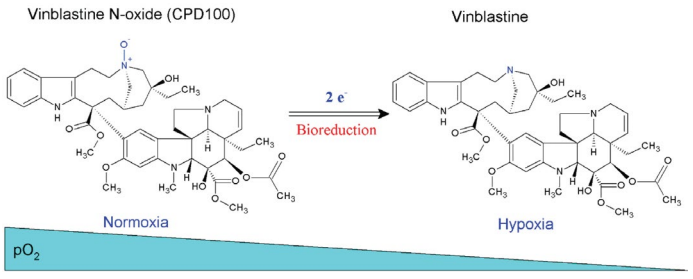

Figure 2. *Schematic representation of bioreduction of prodrug CPD100 to parent drug vinblastine under hypoxic conditions. ©Elsevier*; reproduced by permission.[11]

Experimental Methods

Preparation and Characterization of Liposomes. CPD100Li was prepared using a pH-gradient method utilizing sphingomyelin/cholesterol at 55:45 molar ratios. The lipidic thin film was formed by solvent evaporation and was rehydrated at 65°C for 30 min with 300 mM $MgSO_4$ to form multilamellar vesicles (MLV). The resulting MLVs were extruded and purified using a Sephadex PD 10 column equilibrated with sucrose, 4-(2-hydroxyethyl)-

continued

1-piperazineethanesulfonic acid (HEPES), and ethylenediaminetetraacetic acid (EDTA) buffer (SHE) to generate the large unilamellar vesicles (LUV). CPD100 was loaded into the liposomes in the presence of A23187 ionophore via a pH gradient method.[6]

CPD100Li was characterized using high-performance liquid chromatography (HPLC), cryo-transmission electron microscopy (Cryo-TEM), and dynamic light scattering (DLS).

***In vitro* Cell Proliferation Studies.** The effects of empty liposomes (lipid concentration at 12.5 mM), CPD100Li (lipid concentration 0.5 mM to 2 nM), and CPD100 in dimethyl sulfoxide (DMSO) (lipid concentration 1 mM to 20 nM) were studied in adenocarcinomic human alveolar basal epithelial (A549) cells at two oxygen levels, normoxic (18%) and hypoxic (1.5%). Cell viability was assessed at 72 h using fluorescence measurements per the Cell Titer-Blue® protocol at 550 nm excitation and 590 nm emission. All the experiments were performed in quadruplicate.

***In vivo* Studies**. The dose-limiting toxicity (DLT) and MTD were determined in nude athymic female mice by intravenous (i.v.) administration every 7 days for two cycles with no treatment for 3 weeks after the first cycle, as per the National Cancer Institute (NCI) Developmental Therapeutics Program protocol. Groups included empty liposomes (vehicle, lipid dose = 50 mg/kg), CPD100, and CPD100Li. CPD100Li efficacy was evaluated in an A549 tumor xenograft model with two cycles of dosing, and the percent changes in tumor volume and body weight were monitored for 90 days. The pharmacokinetic profile of CPD100Li was assessed in mice dosed at 30 mg/kg and fitted into a noncompartmental model to determine the clearance, volume of distribution, and circulation half-life.

Results and Discussion

Preparation and Characterization of Liposomes. The CPD100 loading in the CPD100Li was 5.5 mg/mg, and the liposomes were stable for 48 h with a *z*-average diameter of 171 ± 3.44 nm and a polydispersity index (PDI) of 0.095 ± 0.038. Cryo-TEM of the CPD100Li showed the presence of more LUVs compared with MLVs, which were observed in the drug-free liposomes. There was no drug precipitation or electron-dense region in the CPD100Li, which was observed for other liposomal formulations as in CPT-11 and doxorubicin.[7,8] This may be owing to the high hydrophilicity of CPD100, which prevented the precipitation.

***In vitro* Cell Proliferation Studies.** The IC_{50} values (the concentration of an inhibitor at which the response is reduced by half) of CPD100 in normoxia and hypoxia were 24,152 ± 2,185 and 11,600 ± 1,396 nM, respectively. In contrast, the IC_{50} values for CPD100Li in normoxia and hypoxia were 527 ± 99 and 132 ± 18 nM respectively. The empty liposomes at different lipid concentrations produced no antiproliferative effect in A549 cells under normoxic and hypoxic conditions compared with untreated cells. As expected, the data indicated a stronger antiproliferative effect for CPD100 under hypoxic conditions compared with normoxic conditions. The liposomal formulation for CPD100 was more potent than the free compound, possibly owing to a higher drug uptake by the cells due to liposomal encapsulation. Lipid nanocarriers tend to increase the penetration of chemotherapeutic agent inside the cells, and this combined with selective hypoxia activation of CPD100 made them more toxic to the cells.[9,10]

***In vivo* Studies.** The DLT for CPD100 and CPD100Li was 45 mg/kg. The MTD for CPD100 and CPD100Li was 40 mg/kg, indicating that the liposomal formulations did not change the acute toxicity profile of the CPD100. The effect of CPD100Li and CPD100 on the volume of the A549 xenograft model is depicted in Figure 3. The CPD100Li treatment group was significantly lower in the percent increase in the tumor volume of the mice after 90 days compared with other treatment groups (Fig. 3). The median survival of the control and vehicle groups was not statistically different. In contrast, the median survival of the CPD100Li-treated animals was 90 days, compared with the CPD100-treated group. The concentration versus time profile of the sum total of CPD100 in plasma after the administration of CPD100Li and CPD100 is depicted in Figure 4. The circulation time of CPD100Li increased by 13-fold compared with CPD100. This was also accompanied by an increase in the volume of distribution and decrease in clearance of the CPD100Li compared with CPD100, as seen in Table 1.[11]

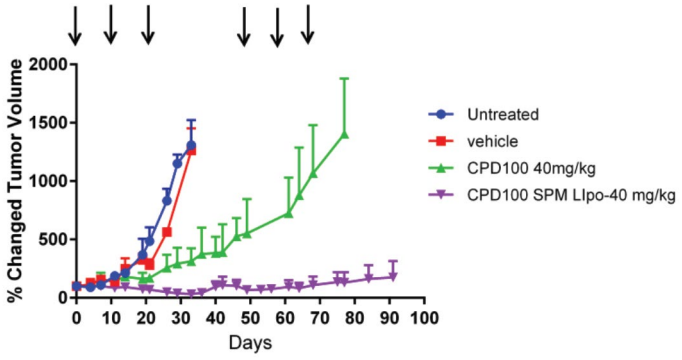

Figure 3. *Xenograft regression in mice over time after i.v. injection of saline (untreated), empty liposome (vehicle), CPD100, and CPD100Li at 40 mg/kg (n = 4/treatment, mean ± standard deviation).* ©Elsevier; reproduced by permission.[11]

In conclusion, the results of our study indicate that the pharmacokinetic and efficacy profile of the first hypoxia-activated prodrug liposomal formulation was superior to that of CPD100 in a non-small cell lung cancer xenograft model. Our results represent a novel and efficacious therapeutic strategy utilizing hypoxia for treatment of lung cancer.

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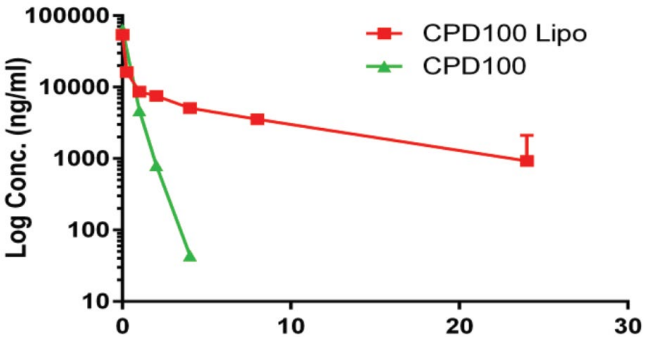

Figure 4. *Plasma concentration of CPD100 in mice after i.v. injection of CPD100Li and CPD100. Data represent the mean ± standard deviation (n = 4).* ©Elsevier; reproduced by permission.[11]

Table 1. Pharmacokinetic Parameters of CPD100 and CPD100Li[a]

Parameters	CPD100	CPD100Li
Dose (mg/kg)	30	30
Cmax (ng/mL)	68,567	54,300
tmax (h)	0.08	0.08
AUClast (h·ng/mL)	32,725	56,254
AUC(0-INF)(h·ng/mL)	32,756	84,221
$t_{1/2}$ (h)	0.44	5.5
Vz_obs (mL/kg)	17.4	2,825
Cl_obs (mL/h/kg)	916	356

[a] After i.v. injection of each at a dose of 30 mg/kg in mice.

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In Vitro and *In Vivo* Evaluation of Controlled Payload Release Using Acoustically Responsive Scaffolds

Alexander Moncion,[a,b] Oliver D. Kripfgans,[a,b,c] Renny T. Franceschi,[c,d,e] Andrew J. Putnam,[c] and Mario L. Fabiilli[a,b]

Introduction

Fibrin hydrogels are protein-based scaffolds frequently used in tissue engineering for delivery of bioactive payloads (e.g., growth factors). Conventional fibrin scaffolds enable very limited spatial and temporal control of payload release, especially after implantation. This is potentially problematic because tissue regeneration is tightly regulated by biomolecules in a spatiotemporal manner.[1] We have designed acoustically responsive scaffolds (ARSs) that will enable on-demand, spatiotemporally controlled payload release from a hydrogel scaffold using focused ultrasound (US) as the triggering mechanism. ARSs are formed by incorporating sonosensitive perfluorocarbon (PFC) double emulsions into the fibrin hydrogels. Sonosensitive PFC emulsions are used because of their biocompatibility, inertness, and acoustic sensitivity. Water-soluble payloads are contained within the W_1 phase, and each interface (i.e., W_1/PFC and PFC/W_2) is stabilized by a nonionic surfactant. Control of payload release from the ARS is achieved using nonthermal US, termed acoustic droplet vaporization (ADV), whereby the PFC phase within the emulsion vaporizes when exposed to US above an acoustic threshold.[2,3] ADV is triggered using focused, megahertz frequency US, which means submillimeter precision is obtainable, even within deep tissue. Most importantly, the use of US to modulate ARSs enables noninvasive controlled release of the encapsulated payload after the scaffold has been implanted.

Methods

Emulsion Preparation. Sonosensitive double emulsions, with the structure water-in-PFC-in-water (W_1/PFC/W_2, mean diameter: 2.1 ± 0.1 μm), were prepared following a previous method.[4] Briefly, a triblock fluorosurfactant, consisting of Krytox synthetic oil and polyethylene glycol (molecular weight [MW]: 1 kDa) was dissolved in 1 g of PFC at 2% (w/w). The PFC phase consisted of perfluorohexane (C6, C_6F_{14}, 56°C boiling point) or a 1:1 admixture of perfluorohexane and perfluoropentane (C5, C_5F_{12}, 29°C boiling point). The PFC solution was then combined, 2:1 (v/v), with an aqueous solution of Alexa Fluor 680-labeled dextran (AF680, MW: 10 kDa) reconstituted at 0.625 mg/mL in Dulbecco's phosphate-buffered saline (DPBS). This concentration of dextran was chosen to prevent self-quenching of the fluorophore. The phases were sonicated for 30 s while on ice. The resulting primary emulsion, with a water-in-PFC (W_1/PFC) structure, was added dropwise to a solution of 50 mg/mL of Pluronic F68 nonionic surfactant in DPBS and stirred at 700 rpm for 2 min while on ice. The particle size of the resulting coarse double emulsion (W_1/PFC/W_2) was reduced using a homogenizer at 29,900 rpm.

ARS Fabrication. ARSs were prepared using 10 mg/mL of clottable protein by first combining bovine fibrinogen dissolved in degassed (36% O_2 saturation) Dulbecco's modified Eagle's medium (DMEM), with bovine thrombin (20 U/mL), 0.025 U/mL of aprotinin, and 1% (v/v) emulsion. ARSs containing emulsion with either the PFC admixture (i.e., C5/C6) or C6 are referred to as C5/C6-ARS and C6-ARS, respectively.

***In Vitro* Release Studies.** For *in vitro* release studies, 0.5 mL of ARSs was cast in 24-well Bioflex plates and covered with 0.5 mL of DMEM. ARSs were exposed to focused US (2.5 MHz, peak rarefactional pressure = 8 MPa, 13 cycles, 100 Hz pulse repetition frequency) for 2 min daily (starting on day 1). To quantify the amount of AF680 released from the ARS, aliquots of the overlying media were sampled throughout the experiment and analyzed with a plate reader.

***In Vivo* Release Studies.** This *in vivo* research was conducted with approval of the Institutional Animal Care and Use Committee at the University of Michigan. ARSs (0.25 mL volume per ARS) were prepared as described previously and injected subcutaneously in the lower back of BALB/c mice and polymerized *in situ*. After polymerization, subsets of the implanted ARSs were exposed to US (same parameters as previously described). Animals were imaged periodically using a preclinical fluorescence imaging system to quantify the dextran signal remaining in each implant.

continued

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[e] Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, MI U.S.A.

Statistics. All statistical analyses were performed with GraphPad Prism software. All data are expressed as the mean ± standard error of the mean of measured quantities. All *n* values are listed below each corresponding figure. Statistically significant differences were determined with a Student's *t* test corrected for multiple comparisons using the Holm–Sidak method, with differences deemed significant for $P < 0.05$.

Results

AF680 was used as the model payload for all experiments because it can be easily quantified both *in vitro* and *in vivo*. Figure 1A shows that on day 5 C5/C6-ARSs exposed to US (i.e., +US) had 33.5 ± 3.3% payload released versus identical ARSs not exposed to US (i.e., –US, 5.5 ± 1.8%). The difference between +US and –US is evident on the initial day of US exposure, with 10.2 ± 1.6% released for +US and 1.2 ± 0.1% for –US. This trend follows for C6-ARSs (Fig. 1B), with 2.8 ± 0.3% released for –US and 19.4 ± 2.4% released for +US on day 5. Both data sets show statistically significant differences between +US and –US starting on day 1. The positive control, which was a conventional 10 mg/mL of fibrin hydrogel containing nonencapsulated AF680, had 84.4 ± 3.1% payload released by day 5.

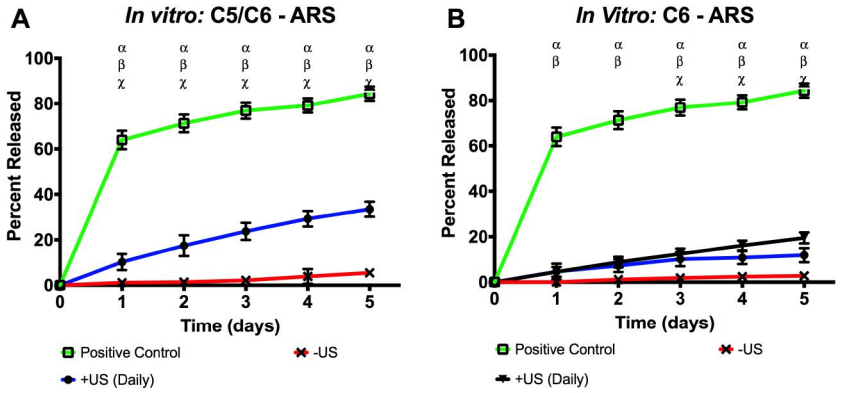

Figure 1. *In vitro release profiles for fibrin scaffolds and ARSs with (A) C5/C6 and (B) C6 emulsion. For both ARS conditions, the release was greater in ARSs exposed to US. The positive control, which consisted of a fibrin scaffold with nonencapsulated dextran, had the most release by day 5. Each condition had n = 5 samples. Significance at $P < 0.05$ indicated as follows: α indicates +US versus –US; β indicates positive control versus +US; and χ indicates positive control versus –US.*

In Figure 2, US caused release of the AF680 payload in the ARS, which was subcutaneously implanted in a mouse. The released payload was absorbed and eventually cleared by the subcutaneous vasculature. The clearance caused a decrease in fluorescence signal, which was monitored noninvasively with a preclinical imaging system. In Figure 3, greater payload release was observed at day 7 for +US ARSs versus –US ARSs (C5/C6: –US, 67.8 ± 1.9% and +US, 89.3 ± 1.0% versus C6: –US, 51.7 ± 9.6% and +US, 85.9 ± 7.1%). Mice with C5/C6-ARSs and C6-ARSs showed statistically significant differences between +US and –US starting on day 1 and day 3, respectively.

Conclusions

Controlled release from an ARS can be achieved using focused US. Both *in vitro* (Fig. 1) and *in vivo* (Figs. 2 and 3) results show that greater dextran release is obtained with +US versus –US. When exposed to identical experimental conditions, C6-ARSs displayed lower nonselective (i.e., –US) and selective (i.e., +US) release compared with the C5/C6-ARSs. This may be due to the greater stability provided by ARSs formulated from a higher boiling point PFC such as C6 (56°C) versus an admixture of C5 (29°C) and C6. Greater payload retention occurred *in vitro* with the –US condition compared with *in vivo*. In particular, Figure 3A shows that on day 1 a large fraction of the payload

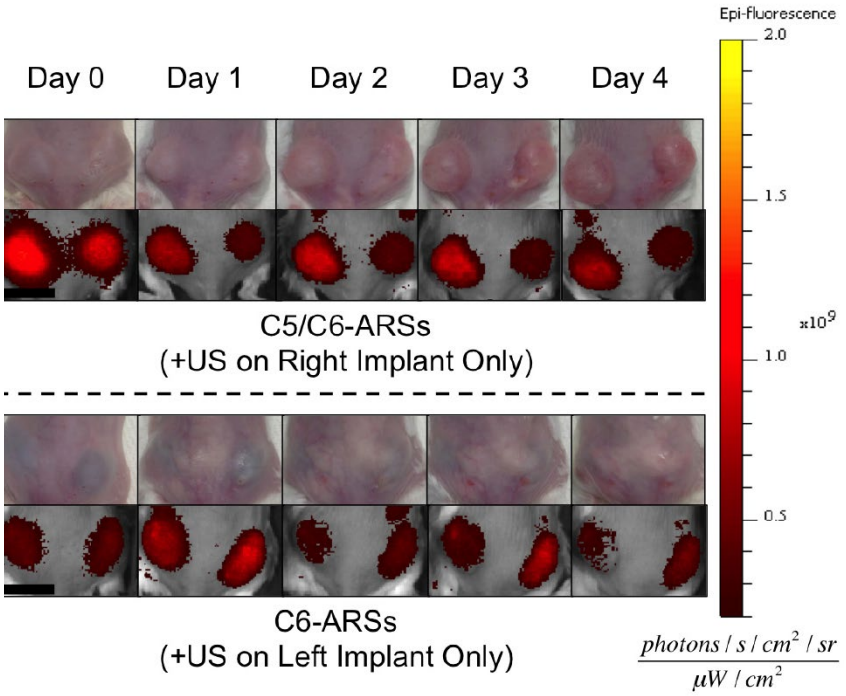

Figure 2. *Longitudinal photographs and fluorescence images of mice with two subcutaneously implanted ARSs (top rows: C5/C6-ARSs; bottom rows: C6-ARSs). The ARSs were implanted on day 0, and US was applied daily starting on day 1 to the right implant (top row) and left implant (bottom row). The photographs show that the ARSs increased in size as a function of time due to the vaporization and in-gassing of the PFC. The fluorescence images show a faster clearance of the payload released from the ARSs exposed to US. The colormap is quantitatively indicative of the AF680 concentration remaining in the ARS. Scale bar = 1 cm.*

continued

was released in the –US condition; however, the addition of US increased the release by more than 9% (absolute). This quick release of payload was not observed in C6-ARSs, which showed no differences between +US and –US until day 3. Future studies will be focused on understanding how various properties of the ARS impact release and applying this controlled delivery system for therapeutic angiogenesis.

Acknowledgements
This work was supported by National Institutes of Health (NIH) grant R21AR065010 (M. L. Fabiilli) and the Basic Radiological Sciences Innovative Research Award (M. L. Fabiilli). A. Moncion was supported by the National Science Foundation Graduate Student Research Fellowship (Grant No. DGE 1256260).

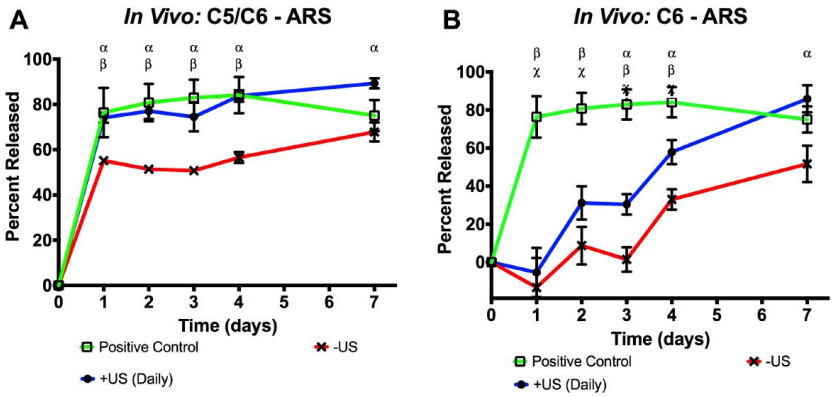

Figure 3. *In vivo release profiles for fibrin scaffolds and ARSs with (A) C5/C6 and (B) C6 emulsion. For both ARS conditions, the release was greater for ARSs exposed to US. The –US conditions had greater payload released than the in vitro counterpart; however, there was more payload retained when compared with the in vivo +US case as well as the positive control. Each condition had n = 8 samples. Significance at P < 0.05 indicated as follows: α indicates +US versus –US; β indicates positive control versus +US; and χ indicates positive control versus –US.*

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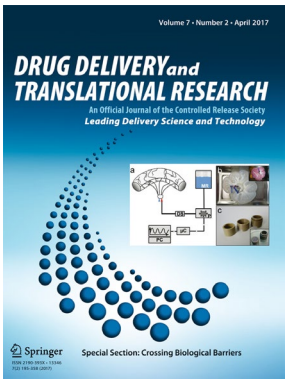
Drug Delivery and Translational Research Update

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

2016 *DDTR* Outstanding Research Paper Award Winner
The Selection Committee and CRS are pleased to announce the following paper published in *DDTR* during 2016 for the award. Criteria such as translation nature of research, overall impact, innovation, and significance of the study were considered in the selection process. The award is jointly sponsored by Springer-Nature and CRS. The corresponding authors will be recognized at the 44th CRS Annual Meeting & Exposition hosted in Boston, Massachusetts, U.S.A., July 16–19, 2017. Please join us in congratulating authors of the paper for their outstanding achievement.



Riboflavin-induced photo-crosslinking of collagen hydrogel and its application in meniscus tissue engineering
Jiseung Heo, Rachel H. Koh, Whuisu Shim, Hwan D. Kim, Hyun-Gu Yim, and Nathaniel S. Hwang
Drug Deliv. Transl. Res. 6(2): 148-158, 2016

In this paper, the authors have tissue engineeried a scaffold that can potentially be used as a meniscus tissue. Meniscus significantly contributes to knee health by playing a critical role in shock absorption, load distribution, and joint stabilization. Meniscus tears are known to occur readily with aging or extreme exercising. However, when it happens the inner region of the meniscus has limited regeneration capacity due to the lack of blood vessels. Numerous studies have been conducted to develop an optimal treatment strategy for meniscus tears, which include allograft transplantation, menisectomy, and meniscus substitution. In this paper, the authors have investigated riboflavin as a photo-sensitizer for photo-crosslinking of collagen hydrogel scaffolds for meniscus tissue engineering. The chemical crosslinking results from the covalent bond formation between amino acids of collagen fibril induced by singlet oxygen generated from light-excited riboflavin. This riboflavin-induced collagen crosslinking mechanism has been approved for clinical application in cornea tissues. As collagen fibers account for 90% w/v of meniscus tissue, their study utilized the riboflavin-induced crosslinking system to enhance the mechanical property and overall stability of collagen-based scaffolds as a clinically safe method. In addition, the group also demonstrated that hyaluronic acid, which has been shown to promote meniscus regeneration, can be incorporated into the collage scaffolds. Furthermore, the results of gene expression analysis and histology suggest that fibrochondrocytes encapsulated in crosslinked collagen hydrogel with hyaluronic acid showed enhanced expression of meniscus tissue related genes and extracellular matrix production. These results indicate that the physically improved collagen hydrogel can be potentially applied.

About the Corresponding Author
Nathaniel S. Hwang (nshwang@snu.ac.kr) is currently an associate professor in the School of Chemical and Biological Engineering at Seoul National University, Republic of Korea. Since March 2017, he has been the director of the Interdisciplinary Graduate Program in Bioengineering, and he is also a member of the Institute for Chemical Processes at Seoul National University and the Stem Cell Graduate Program at the Seoul National University, Republic of Korea. Dr. Hwang received a bachelor's degree in biomedical engineering from Johns Hopkins University Whiting School of Engineering in 2002. He obtained his Ph.D. in biomedical engineering from the Johns Hopkins School of Medicine in 2007 under the guidance of Prof. Jennifer Elisseeff. After doctoral studies, he was a visiting scholar at the University of California, San Diego, Department of Bioengineering, and worked with Prof. Shyni Varghese. From 2008 through 2011, he worked as a postdoctoral associate in Prof. Robert Langer's laboratory at Massachusetts Institute of Technology. In 2011, Dr. Hwang joined the School of Chemical and Biological Engineering at Seoul National University.

Dr. Hwang is currently leading a group of students that work together to develop new biomaterials, study stem cells, and design new technologies for regenerative medicine. In particular, Dr. Hwang's laboratory is working toward the fabrication of bio-synthetic microenvironments conducive to stem cell differentiation by manipulating scaffold properties and incorporating the desired biological signals. In addition, Dr. Hwang's laboratory is developing non-viral strategies for a direct conversion stem cell technology. He has published over 66 research articles and book chapters covering biomaterials and stem cells for musculoskeletal tissue regeneration.

Join the leading scientists who are publishing their work in *DDTR* and also compete for the 2017 *DDTR* outstanding research/clinical paper award. The paper will be selected from the research articles/clinical research/clinical trials published in *DDTR* during 2017. The award will be presented in 2018 during the 45th CRS Annual Meeting. Visit the CRS website for the award criteria (www.controlledreleasesociety.org/about/Awards/Pages/DDTROustandingPaper.aspx). ■

People in the News

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

Veteran Biotech Executive Timothy S. Nelson Joins Impel's Board of Directors

Business Wire: March 3, 2017 – SEATTLE, WA, U.S.A. – Impel NeuroPharma, a Seattle-based clinical-stage biotechnology company developing first-in-class intranasal drug treatments, announced today the appointment of Timothy S. Nelson as independent director of the board of directors.

Mr. Nelson has over 20 years of experience with drug delivery, medical devices, and drug-device combinations. Most recently, Mr. Nelson served as MAP Pharmaceuticals' president and CEO and as a member of its board of directors from April 2005 until March 2013. MAP was acquired by Allergan for $960 million. During that time, Mr. Nelson led the company through its initial public offering and developed LEVADEX, an inhaled dihydroergotamine for migraine. Prior to MAP, he served as senior vice president of commercial and business development at DURECT Corporation and has held various senior management positions with Medtronic, including business director of the neurological division for Europe, the Middle East, and Africa, and as manager of drug delivery ventures.

Mr. Nelson has served on several boards, including chairman of the board of Civitas, a private biopharmaceutical company focused on treating undermet medical needs in neurological indications from December 2013 to October 2014. The company was acquired by Acorda Therapeutics for $525 million that year. He also served on the board of directors of Surmodics, a public medical technology company, from February 2014 to March 2015. Mr. Nelson holds a master's degree in management with distinction from the Kellogg Graduate School of Management at Northwestern University and a bachelor's degree in chemical engineering from the University of Minnesota.

"We are very excited to bring Tim onto Impel's board of directors. Tim brings a deep knowledge of both medical devices and pharmaceutical products that will help Impel drive clinical development of our drug-device combination products," said John Hoekman, Impel's founder and CEO. "Impel is developing nasally administered products to treat migraine, Parkinson's, and Alzheimer's disease. Tim's experience and leadership will help Impel advance these therapies through clinical testing and into the hands of patients."

"Impel's unique, cutting-edge technology has the potential to make a substantial step forward in more effective delivery of drugs that can mean better outcomes for millions of patients who are underserved by existing therapies," Mr. Nelson said. "I am very pleased to be able to contribute to Impel's mission and growth."

Impel NeuroPharma's POD™ nasal drug delivery platform is designed to deliver drugs to the upper nasal cavity for improved biodistribution. By delivering therapeutics to the upper nasal cavity, the POD nasal delivery platform takes advantage of the vascular-rich olfactory region for improved bioavailability and has the potential to target the brain via the olfactory and trigeminal nerves. Delivery of therapeutically meaningful levels of drugs may allow for development of more effective drugs and expand the range of treatment options available to patients.

Impel NeuroPharma, Inc., is a Seattle-based company developing intranasal drug treatments for central nervous system (CNS) disorders. Impel NeuroPharma has developed a novel drug delivery platform, the POD™ technology, that administers drug to the deep nasal cavity to improve the biodistribution of many drugs. Impel NeuroPharma's proprietary (POD) device technology enables entirely new categories of drugs, including biologics, to be administered using a cost-effective, disposable, non-invasive intranasal drug delivery device. To learn more about Impel NeuroPharma, please visit our website: http://impelnp.com. ■

Companies in the News

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

March

Merrimack Initiates Phase 1 Study of MM-310 in Solid Tumors

PRNewswire: March 23, 2017 – CAMBRIDGE, MA, U.S.A. – Merrimack Pharmaceuticals, Inc. (NASDAQ: MACK) today announced the enrollment of its first patient in a phase 1 study of MM-310 in solid tumors. MM-310 is an antibody-directed nanotherapeutic (ADN) that encapsulates a novel taxane and targets the EphA2 receptor, a protein which surveys suggest is overexpressed in 50–100% of many major tumor types, including prostate, ovarian, bladder, gastric, pancreatic, and lung cancers.

"The initiation of this study is an important step in evaluating MM-310's safety and preliminary activity in patients diagnosed with solid tumors," said Vasileios Askoxylakis, MD, PhD, medical director and MM-310 project leader at Merrimack. "MM-310 was designed to maximize targeted delivery and local activation of a newly engineered and proprietary prodrug of docetaxel, a broadly used potent chemotherapy that is often associated with significant drug-related toxicities, with a goal of minimizing exposure to healthy tissue. In several preclinical models, MM-310 not only demonstrated superior antitumor activity when compared to free docetaxel, but also fewer hematologic toxicities. We look forward to continuing MM-310's development via this study."

The phase 1 open-label study will assess the safety, pharmacology, and preliminary activity of MM-310 in three parts. In part one, MM-310 will be assessed as a monotherapy until a maximum tolerated dose (MTD) is established. After the MTD of MM-310 is established, the study will include two further concurrent parts consisting of an expansion cohort as a single agent and a dose-finding phase in combination with other therapies. Merrimack expects to report data from part one of the study in 2018. Five sites are currently expected to participate in this study. The first patient was dosed at Honor Health in Scottsdale, Arizona.

MM-310 is an antibody-directed nanotherapeutic (ADN) that encapsulates a novel prodrug of the highly potent chemotherapy docetaxel in an ephrin receptor A2 (EphA2)-targeted liposome. EphA2 receptors are shown to be overexpressed in several solid tumors, including prostate, ovarian, bladder, gastric, pancreatic and lung cancers. Moreover, EphA2 receptors are associated with poor outcomes in certain indications. Preclinical data on MM-310 were presented in an oral presentation and three poster sessions at the 2016 American Association for Cancer Research (AACR) Annual Meeting, and further data will be presented at the 2017 AACR Annual Meeting in April. For more information on the phase 1 study in solid tumors, please visit www.clinicaltrials.gov (identifier: NCT03076372).

Merrimack is a biopharmaceutical company based in Cambridge, Massachusetts, that is outthinking cancer to ensure that patients and their families live fulfilling lives. Our mission is to transform cancer care through the smart design and development of targeted solutions based on the deep understanding of cancer pathways and biological markers. All of our product candidates, including three in clinical studies and several others in preclinical development, fit into our three-pronged strategy of 1) understanding the biological problems we are trying to solve, 2) designing specific solutions, and 3) developing those solutions in biomarker-enriched homogenous patient populations. Through systems biology, which brings together the fields of biology, computing, and engineering, Merrimack aims to decrease the uncertainty in drug development and clinical validation. Such an approach has the potential to make individualized treatment of patients a reality. For more information, please visit Merrimack's website at www.merrimack.com.

Effective One-Shot Vaccination of Newborns Moves Closer to Reality

PRNewswire: March 23, 2017 – BOSTON, MA, U.S.A. – Newborns are highly vulnerable to infections and don't respond optimally to most vaccines because their young immune systems typically mount weak antibody responses. Now, researchers at Boston Children's Hospital report achieving strong vaccine responses in newborn animals, including monkeys—the final preclinical model before human trials—by adding compounds known as adjuvants that boost the immune response. In two simultaneous papers, they also describe improved adjuvant formulations that could reduce side effects.

Globally, vaccines that could be given at birth could sharply reduce infant mortality. However, currently, only BCG, polio vaccine, and hepatitis B vaccines are effective in newborns, and the latter two require multiple doses for protection. The new studies, led by David Dowling, PhD, cap a decade of research in the laboratory of Ofer Levy, MD, PhD, aimed at tailoring vaccines to newborns' unique immune systems. They were published March 23, in the *Journal of Clinical Investigation–Insight* (*JCI–Insight*) and the *Journal of Allergy and Clinical Immunology* (*JACI*).

continued

"Our efforts to understand the biology of the newborn immune system have now led to adjuvant approaches that may enable earlier protection of newborns and young infants from life-threatening infectious diseases, such as pneumococcus, pertussis or even respiratory syncytial virus (RSV)," says Levy, director of the Precision Vaccines Program in Boston Children's Hospital's Division of Infectious Diseases and senior investigator on both studies.

Pneumococcal vaccine was used as a test case because it can cause potentially fatal pneumonia, meningitis, and sepsis in infants. In the first study (*JCI-Insight*), newborn Rhesus monkeys were given a series of three shots with the existing Prevnar 13 pneumococcal vaccine. This vaccine is already packaged with an adjuvant (alum), but half the monkeys were randomized to also receive an adjuvant called 3M-052 that Levy, Dowling, and colleagues have shown to activate newborn immune responses. Blood was drawn at different time points to see how well the immune system was responding.

At day 28, even before receiving the second dose with 3M-052, the animals were much quicker to develop an antibody response, and their antibody levels were 10 to 100 times greater than that with Prevnar 13 alone—high enough to ensure protection against infection. They also showed dramatically enhanced CD4+ T cells and B cells specific to *Streptococcus pneumoniae*. (Monkey experiments were conducted at the Tulane National Primate Research Center.)

"The protective antibody response we saw was so strong that it is conceivable that you could get protection with one shot," says Levy. "This is critical because in many parts of the world, birth is the most reliable point of healthcare contact. After birth, it becomes challenging to bring children in for repeated clinic visits."

The adjuvant works by stimulating a set of receptors on white blood cells known as Toll-like receptors (TLRs). Research by the Levy Lab has found that stimulating two of these receptors, TLR7 and TLR8, induces the strongest antibody response.

Studying white blood cells derived from newborns' umbilical cords, the researchers also saw robust T helper 1-cytokine production when given 3M-052 alone. When it was added to Prevnar 13, the response was synergistic.

The 3M-052 adjuvant used for this monkey study, manufactured by 3M Drug Delivery Systems, is designed to minimize side effects: it is configured chemically with a lipid "tail" that mixes poorly with water. This keeps it from getting into the bloodstream, where it could cause inflammation and flu-like symptoms.

"Rather than floating all over the place causing fever and chills, when you inject this 3M-052 adjuvant, it stays put in the muscle and enhances the immune response to the vaccine," says Levy.

The second study, co-led by Jeffrey Hubbell, PhD, of École Polytechnique Fédérale de Lausanne in Switzerland (now at University of Chicago), used a different adjuvant approach described in the *JACI* paper. To both maximize immune response and avoid systemic inflammation, the researchers encapsulated the vaccine antigen and a TLR8-activating adjuvant named CLO75 in nanoparticles. The particles were specially engineered to be taken up by antigen-presenting cells, which instruct lymphocyte cells to make antibodies.

When added to human cells in a dish and when injected into mice that express the human TLR8 gene, the nanoparticles stimulated immune responses that were as good or better than those induced by the BCG vaccine—one of the few vaccines that works in newborns.

The team's next steps are to develop a highly stable formulation, obtain more safety data, and further characterize age-specific responses, comparing newborns versus older infants. Levy plans to work with collaborators from around the world, via the Precision Vaccines Program he founded last year, to work towards eventual human trials.

"There's not a long list of vaccines that can be given at birth, and we need better vaccine formulations against a range of early life infectious pathogens," says Levy. "We hope to meet these challenges."

David Dowling, PhD, of Boston Children's was first author of the *JCI-Insight* paper. Dowling and Evan Scott, PhD, of Northwestern University, were co-first authors of the *JACI* paper. Jeffrey Hubbell, PhD, was co-senior author on the *JACI* paper. The research was funded by the Bill & Melinda Gates Foundation, the National Institutes of Health/NIAID, the European Research Council, and Boston Children's Hospital. The Levy Laboratory also received sponsored research support from 3M Drug Delivery Systems.

continued

Intec Pharma Initiates Phase I Trial of Accordion Pill for Cannabinoid Therapies

PRNewswire: March 22, 2017 – JERUSALEM, Israel – Intec Pharma Ltd. (Nasdaq; TASE: NTEC), a clinical stage biopharmaceutical company focused on developing drugs based on its proprietary Accordion Pill™ platform technology, announces the initiation of a phase I clinical trial of AP-CBD/THC, its Accordion Pill platform with the two primary cannabinoids contained in *Cannabis sativa*, cannabidiol (CBD) and tetrahydrocannabinol (THC), which is being developed by Intec for various indications, including low back pain and fibromyalgia.

The *Cannabis sativa* plant is used in treatment of chronic pain and a variety of other indications. Previous clinical studies conducted using the whole plant or specific extracts generated evidence of the cannabis analgesic activity. Furthermore, extracts containing known amounts of the active plant driven compounds (mainly THC and CBD) or diverse synthetic THC derivatives are promising treatments for painful conditions that do not respond properly to currently available treatments, such as chronic, neuropathic, and inflammatory pain.

AP-CBD/THC holds the potential to address several major drawbacks of current methods of use and treatment with cannabis and cannabinoids, such as short duration of effect, delayed onset, variability of exposure, variability of the administered dose, and adverse events that correlate with peak levels. AP-CBD/THC is designed to extend the absorption phase of CBD and THC, resulting in more consistent levels, for an improved therapeutic effect.

This phase I trial is a single-center, single-dose, randomized, three-way crossover study to compare the pharmacokinetics, safety, and tolerability of two formulations of AP-CBD/THC, with Buccal Sativex®, in 21 normal healthy volunteers. Sativex is a commercially available oral buccal spray containing CBD and THC. The company expects to have topline results from this trial in the third quarter of 2017.

"The progression of AP-CBD/THC into the clinic is a significant achievement for Intec and marks a major step forward in developing a potential new therapy for pain management. It is also our first demonstration of the Accordion Pill platform for cannabinoid therapies. Moving forward, we plan to evaluate the Accordion Pill platform in several other indications where a safe, effective, prolonged, and consistent cannabinoid therapy may be able to provide therapeutic benefit where other treatments have failed. We are very pleased to have initiated our phase I trial with AP-CBD/THC," stated Zeev Weiss, chief executive officer of Intec Pharma.

The cannabis market has significant commercial potential and is projected to represent approximately 10% of the specialty pharmaceutical market over the next five years, or a market of at least $20 billion. According to Global Data, in 2016 the global low back pain drug market was $6.2 billion and the global fibromyalgia drug market was $1.8 billion.

Intec Pharma Ltd. is a clinical stage biopharmaceutical company focused on developing drugs based on its proprietary Accordion Pill platform technology. The company's Accordion Pill is an oral drug delivery system that is designed to improve the efficacy and safety of existing drugs and drugs in development by utilizing an efficient gastric retention and specific release mechanism. The company's product pipeline currently includes three product candidates in clinical trial stages: Accordion Pill Carbidopa/Levodopa, or AP-CDLD, which is being developed for the indication of treatment of Parkinson's disease symptoms in advanced Parkinson's disease patients, Accordion Pill Zaleplon, or AP-ZP, which is being developed for the indication of treatment of insomnia, including sleep induction and the improvement of sleep maintenance, and an Accordion Pill that is being developed for the prevention and treatment of gastroduodenal and small bowel nonsteroidal anti-inflammatory drug (NSAID) induced ulcers.

EnGeneIC Doses First Patient in U.S. Phase 1 Clinical Study of Targeted EDV™ Nanocells in Recurrent Glioblastoma Multiforme

PRNewswire: March 21, 2017 – NEW YORK, NY, U.S.A. and SYDNEY, Australia – EnGeneIC Limited today announced that it has begun dosing patients in a U.S.-based open-label phase 1 clinical trial evaluating its proprietary EDV™ nanocells to treat recurrent glioblastoma multiforme (GBM) in adults.

GBM is the most common primary malignant brain tumor in adults in the United States, accounting for approximately 16% of all primary brain tumors. These patients almost invariably relapse, and there are few treatment options available for recurrent GBM.

Himanshu Brahmbhatt, Ph.D., joint-CEO and director of EnGeneIC, stated, "The Cerebral EDV study is a very exciting trial since for several decades the blood brain barrier (BBB) has been thought to be the limiting factor in allowing anti-tumor drugs to safely get to brain tumor cells. The EDV nanocells bypass the BBB, get into the brain tumor via the tumor-associated leaky blood vessels, and then deliver the toxic payload in therapeutically significant concentrations inside the cancer cells. This allows us to send potent drugs

continued

directly into brain cancer cells, and in previous trials we have witnessed minimal to no toxicity in patients. We call our EDV platform a cyto-immuno-therapeutic since it not only directly targets and kills cancer cells but also stimulates the patient's immune system to 'wake up' and fight the tumor."

The open-label phase 1 Cerebral EDV study is a two-part clinical trial in approximately 20 adults diagnosed with recurrent GBM who have already received first-line chemotherapy. The first part of the study, which will be a dose exploration study, will assess the safety of multiple doses of (EGFR)-EDV-doxorubicin at two dose levels, administered once a week for 7 weeks. The second part of the study will provide guidance on the recommended phase 2 dose of (EGFR)-EDV-doxorubicin. The primary objective of the study is to assess the safety of the therapy, while secondary endpoints include assessing anti-tumor response rates and overall survival, as well as to identify the recommended phase 2 dose. In addition, the study will assess biomarkers associated with immunotherapy aspects of (EGFR)-EDV-doxorubicin. More information regarding the Cerebral EDV trial can be found by visiting https://clinicaltrials.gov/ct2/show/NCT02766699?term=Cerebral+EDV&rank=1.

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in adults in the United States, accounting for approximately 16% of all primary brain tumors. More than 11,000 new cases of GBM are projected for 2017 in the United States. Despite an aggressive multimodal approach of surgery and chemotherapy and/or radiation, relapse is almost inevitable for patients with GBM (approximately 90% recurrence rate). Outcomes for patients with GBM are poor despite best management, and median overall survival for recurrent glioma is less than four months.

EnGeneIC is a clinical stage biopharmaceutical company focused on developing its proprietary bacterially derived EDV™ nanocells as a powerful nanoparticle drug, siRNA, or miRNA delivery platform designed to directly target and effectively kill tumor cells with minimal toxicity, while simultaneously stimulating the immune system's natural and adaptive anti-tumor response. The EDV™ nanocell platform has shown promising results in early clinical studies, and EnGeneIC is currently planning to commence further clinical trials in several cancer indications in Australia and the United States. For more information, please visit www.engeneic.com.

Pulmatrix Receives European Patent for Its Inhaled Drug Delivery Technology

PRNewswire: March 21, 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 received a key patent from the European Union.

"This new patent shows our continued ability to obtain patents that protect our unique iSPERSE inhaled drug technology—and that also reflect the advances we are making in drug delivery," said Robert W. Clarke, Ph.D., chief executive officer for Pulmatrix. "It gives us a strong intellectual property protection position in Europe as we move forward with our drug candidates for COPD, fungal infections, and other diseases."

The new EU patent (EP 2410981 B1) follows on similar patents that Pulmatrix has been granted in the United States and Japan. The most important of those patents is U.S. 9,433,576, which gives broad protection to Pulmatrix's innovative drug delivery technology—and to its use to treat a wide variety of diseases.

These patents explain that delivering drugs directly to the lungs offers numerous advantages. But the full potential can't be realized unless most of the drug actually gets to the lungs, rather than being stuck in the throat or mouth, causing side effects. Pulmatrix's technology uses dry powders that "fly" easily into the lungs, making the delivery much more efficient. In addition, the technology can deliver much larger doses of drugs—and many more different types of drugs—than existing methods can.

"This new patent means that we are now protected from competitors copying our advances in Europe, as well as in the United States," added Dr. Clarke.

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 lung diseases, including opportunities in major pulmonary diseases through collaborations, like PUR0200, a branded generic in clinical development for chronic obstructive pulmonary disease (COPD), and PUR1900, an inhaled antifungal that could benefit severe asthmatics and patients with rare disease like cystic fibrosis. 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.

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Crescita Therapeutics™ Announces Signing of a Licensing Agreement Utilizing Its MMPE™ Technology

PRNewswire: March 21, 2017 – MISSISSAUGA, ON, Canada – Crescita Therapeutics Inc. (TSX: CTX) (Crescita or the company), a commercial dermatology company with a portfolio of non-prescription skincare products and prescription drug products for the treatment and care of skin conditions and diseases and their symptoms, today announced it has signed an exclusive license agreement with a U.S.-based, major dermatological contract research company (CRO) (the licensee) to develop prescription treatments of skin diseases utilizing Crescita's patented Multiplexed Molecular Penetration Enhancer (MMPE™) technology.

Under the terms of the agreement, the licensee will be responsible for developing up to three dermatological products. The licensee will oversee and fund the cost of all development activities until commercialization partner(s) for the products are secured. Crescita is entitled to a share of royalties and other consideration received by the licensee from such partners based on a formula that includes compensation to Crescita for granting the licensee the exclusive license to the MMPE technology.

"This agreement is a good illustration of Crescita's continuing ability to capitalize on our existing drug technologies, as we work to build the non-prescription side of the business," said Dan Chicoine, Crescita's chairman and interim CEO. "Crescita will not incur any research and development costs under the terms of the license, but the company stands to gain an attractive return if the development activities of our licensing partner are successful."

The MMPE technology uses synergistic combinations of pharmaceutical excipients included on the FDA's Inactive Ingredient Guide for improved topical delivery of active pharmaceutical ingredients (APIs) into or through the skin. The benefits of this technology include the potential for increased penetration of APIs with the possibility of improved efficacy, lower API concentration, and/or reduced dosing. Issued U.S. patents provide intellectual property protection through March 6, 2027.

Crescita (TSX: CTX) is a publicly traded, Canadian commercial dermatology company with a portfolio of non-prescription skincare products and prescription drug products for the treatment and care of skin conditions and diseases and their symptoms. Crescita owns multiple proprietary drug delivery platforms that support the development of patented formulations that can facilitate the delivery of active drugs into or through the skin. Crescita's board of directors and management team have demonstrated success in building Crescita's predecessor company, Nuvo Research Inc., including developing multiple drugs that are now approved and commercialized and negotiating multiple licensing transactions. For additional information, please visit www.crescitatherapeutics.com.

Novaliq GmbH Announces Licensing Agreement with AFT Pharmaceuticals for the Distribution of NovaTears®

Business Wire: March 20, 2017 – HEIDELBERG, Germany – Novaliq, a specialty pharmaceutical company with a disruptive drug delivery platform that transforms poorly soluble drugs into effective therapeutics for ophthalmology, today announced a strategic licensing agreement with AFT Pharmaceuticals (AFT) for the commercialization of Novaliq's lead product, NovaTears®, in Australia and New Zealand.

NovaTears is Novaliq's first commercially available ophthalmic product for the treatment of evaporative dry eye diseases (DEDs). In Europe, NovaTears is distributed by URSAPHARM under the brand name EvoTears®.

Under the terms of the agreement, Novaliq has granted AFT an exclusive license for the commercialization of NovaTears across Australasia. In return for these rights, Novaliq will receive an undisclosed upfront payment and royalties on net sales of NovaTears.

"Novaliq is delighted to collaborate with AFT, a leading and innovative pharmaceutical company with a strong commitment to eye care," said Christian Roesky, PhD, CEO, Novaliq. "NovaTears provides a highly differentiated and clinically validated treatment option that significantly improves the signs and symptoms of evaporative DED and Meibomian gland dysfunction (MGD), highly underserved diseases. We are confident that dry eye patients in Australasia will greatly benefit from the use of NovaTears and our partnership with AFT."

"AFT is dedicated to bringing innovative products to market that make a real difference to people's health," said Hartley Atkinson, MD, CEO, AFT. "The addition of NovaTears to our eye care line will be welcomed by doctors and patients alike. It's a first-in-class, water-free, and preservative-free treatment based on Novaliq's proprietary EyeSol® technology platform. NovaTears supports the lipid layer of the tear film by its ability to quickly spread and be absorbed into the eye. We believe that this feature—combined with its small droplet size—will provide superior benefits to patients with evaporative dry eye disease."

NovaTears, the first product developed and commercialized that incorporates Novaliq's proprietary EyeSol technology, is an innovative multi-dose, non-aqueous, and preservative-free topical eye drop for the lubrication of the ocular surface. The NovaTears droplet forms

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a thin and smooth protecting film supporting the lipid layer in its function to prevent tear evaporation for the relief of dry eye and irritated eye symptoms. NovaTears has been classified as a class IIa medical device and received CE mark approval in Europe in July 2013. Open, prospective, uncontrolled post-market clinical studies NT-001 and NT-002 successfully demonstrated safety and significant improvement in signs and symptoms of dry eye disease and Meibomian gland dysfunction. All results of the study point towards excellent clinical performance, safety, and very high convenience and acceptance of NovaTears for patients suffering from hyper-evaporative dry eye.

AFT, founded in 1997, is an Auckland, New Zealand-based pharmaceuticals company operating in Australia, New Zealand, and the Pacific Islands. AFT is listed on the Australian (ASX) and New Zealand (NZX) stock exchanges since December 2015 and has significant local sales operations in Australasia together with R&D activities in pain, orphan drugs, and medical devices.

Novaliq GmbH, founded in 2004, is a Heidelberg-based specialty pharmaceutical company focused on ophthalmology. Its mission is to transform poorly soluble drugs into effective ocular therapeutics for both the front and the back of the eye. Novaliq's proprietary EyeSol technology enhances the topical bioavailability, stability, and safety of traditionally insoluble or unstable drugs, improving the delivery, efficacy, and convenience of treatments for ocular surface diseases including dry eye through preservative-free and multi-dose formulations. Novaliq's most advanced product is NovaTears® with CE marking based on Novaliq's proprietary EyeSol technology. NovaTears is marketed under the brand name EvoTears® in Europe. More on www.novaliq.com.

New Publication Describes Positive Patient Experience in Study of Ocular Therapeutix's Dextenza™ Following Cataract Surgery

Business Wire: March 15, 2017 – BEDFORD, MA, U.S.A. – Ocular Therapeutix, Inc. (NASDAQ: OCUL), a biopharmaceutical company focused on the development, manufacturing, and commercialization of innovative therapies for diseases and conditions of the eye, today announced positive results of a patient experience study of Dextenza™ (dexamethasone insert) 0.4 mg for intracanalicular use. The study, published in *Patient Preference and Adherence*, evaluated the overall patient experience and perceived value of Dextenza following cataract surgery.

Dextenza is a hydrogel-based drug-eluting intracanalicular insert that incorporates the U.S. Food and Drug Administration (FDA)-approved corticosteroid dexamethasone as the active ingredient. Inserted non-invasively through the punctum, Dextenza resides within the canaliculus and delivers dexamethasone to the ocular surface for approximately 30 days. Following the completion of treatment, Dextenza resorbs and exits the nasolacrimal system without need for removal.

The goal associated with Dextenza is to reduce the patient burden of administration of topical eye drops following ophthalmic surgery by enabling the physician to control the entire course of steroid therapy with a single administration. The extended release benefit of Dextenza replaces the need for patients to administer steroid eye drops in a complex, tapering, several-times-a-day regimen over the course of a month. In parallel, Dextenza aims to remove the issues commonly associated with non-compliance of post-operative medications following ophthalmic surgery.

A New Drug Application (NDA) for Dextenza is currently under review by the FDA for the treatment of ocular pain occurring after ophthalmic surgery. The FDA has set a PDUFA target action date for July 19, 2017.

The patient experience retrospective study was conducted with 25 patients who had received active treatment in the company's phase 3 clinical trials of Dextenza for the treatment of post-surgical ocular pain and inflammation.

- All patients reported that the intracanalicular insert was comfortable.
- Ninety-six percent (96%) felt the insert was extremely or very convenient compared to topical eye drops on a tapered schedule.
- Ninety-two percent (92%) reported the highest level of overall product satisfaction, with eighty-eight percent (88%) saying they would request the insert if they were to undergo cataract surgery again.
- Ninety-two percent (92%) of patients surveyed said they would recommend Dextenza to friends or family members.

"We are encouraged by the experiences these patients shared, which add another dimension to the clinical results achieved in the phase 3 clinical trials," said Jonathan H. Talamo, M.D., chief medical officer of Ocular Therapeutix. "If approved, we believe that Dextenza, which incorporates the company's proprietary hydrogel platform technology, will offer an attractive alternative to the current post-operative standard of care of steroid eye drops for those recovering from ophthalmic surgery."

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In the company's third and most recent phase 3 clinical trial, Dextenza successfully met the two primary efficacy endpoints, absence of ocular pain on day 8 and absence of ocular inflammation on day 14, when compared to placebo. Dextenza has exhibited a favorable safety profile and has been well tolerated in all clinical trials, regardless of indication. Subject to the approval of the NDA for post-surgical ocular pain by the FDA, Ocular Therapeutix intends to submit an NDA supplement for Dextenza to broaden its label to include a post-surgical inflammation indication.

Dextenza™ (dexamethasone insert) 0.4 mg for intracanalicular use is placed through the punctum, a natural opening in the eye lid, into the canaliculus and is designed to deliver dexamethasone to the ocular surface for up to 30 days. Following treatment, Dextenza resorbs and exits the nasolacrimal system without need for removal. The company has completed three phase 3 clinical trials with Dextenza for the treatment of post-surgical ocular inflammation and pain.

In January, Ocular Therapeutix resubmitted an NDA to the FDA for Dextenza for the treatment of ocular pain occurring after ophthalmic surgery. The FDA has set a PDUFA target action date for July 19, 2017. Subject to the approval of the NDA for post-surgical ocular pain by the FDA, Ocular Therapeutix intends to submit an NDA supplement for Dextenza to broaden its label to include a post-surgical inflammation indication. Dextenza is also in phase 3 development for the treatment of ocular itching associated with allergic conjunctivitis.

Ocular Therapeutix, Inc., is a biopharmaceutical company focused on the development, manufacturing, and commercialization of innovative therapies for diseases and conditions of the eye using its proprietary hydrogel platform technology. Ocular Therapeutix's lead product candidate, Dextenza™ (dexamethasone insert) 0.4 mg for intracanalicular use, has completed phase 3 clinical development for the treatment of ocular pain and inflammation occurring after ophthalmic surgery. The FDA has accepted the company's NDA resubmission for Dextenza for the treatment of ocular pain occurring after ophthalmic surgery and has established a target PDUFA date of July 19, 2017. Ocular Therapeutix is also pursuing additional indications for Dextenza. OTX-TP (travoprost insert) is in phase 3 clinical development for glaucoma and ocular hypertension. Ocular Therapeutix is also evaluating injectable drug delivery depots for back-of-the-eye diseases. Ocular Therapeutix's first product, ReSure® Sealant, is FDA-approved to seal corneal incisions following cataract surgery.

TA Associates Announces Investment in Ideal Cures

Business Wire: March 14, 2017 – BOSTON, MA, U.S.A., and MUMBAI, India – TA Associates, a leading global growth private equity firm, today announced it has completed an investment in Ideal Cures Private Limited, a supplier of ready-to-use coating products and excipients for tablets and capsules to the pharmaceutical and allied industries. Financial terms of the transaction were not disclosed.

Founded in 1999 in India, Ideal Cures' products are used to provide aesthetic coatings as well as functional coatings for tablets and capsules. Aesthetic sugar or film coatings allow for swallowability and taste masking. They also aid brand recognition, authentication, and differentiation. Functional coatings serve a number of purposes ranging from moisture, oxygen, and light protection of drugs to controlling drug delivery to a specific part of the gastrointestinal tract. Ideal Cures also produces specialty excipients such as neutral pellets, cooling compounds, taste masking agents, controlled release polymer blends, and pharma acrylic polymers. Ideal Cures has three manufacturing plants located in Vasai, Jammu, and Khambat and two state-of-the-art R&D facilities in Mumbai and Vasai. Another plant is under construction in Sikkim.

"We believe that Ideal Cures has a robust business strategy and over the last few years has emerged as a provider of high-quality products and services in the tablet coating space, with a vast and diversified customer base globally," said Dhiraj Poddar, country head of India, TA Associates Advisory Private Limited, who will join the Ideal Cures board of directors. "Ideal Cures has worked diligently to innovate solutions that meet the needs of the pharmaceutical and allied industries, building exceptional manufacturing, research and development, and technical services capabilities to rapidly expand their operations. We are thrilled to have the opportunity to partner with Ideal Cures, and we look forward to helping their experienced team to drive growth."

TA Associates believes that the trend is to outsource the production of ready-to-use, fully formulated coatings, which is being driven most notably by companies seeking innovative solutions that reduce processing time and a company's carbon foot print such as Ideal Cures provides.

"To be a preferred global supplier of coatings and excipients, we have made it our mission over the course of our more than 15-year history to provide our customers with pioneering research and development, excellent technical support and good manufacturing practices," said Suresh Pareek, founder and managing director of Ideal Cures. "We are confident that TA Associates' experience of

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investing in the healthcare sector will provide the financial and operational expertise to help us expand upon our solutions. We are pleased to welcome TA's investment and look forward to benefitting from this partnership."

"Ideal Cures' business, which is focused on innovation, best-in-class products, state-of-the art facilities, and a well-trained and committed professional workforce, continues to evolve," said Kamlesh Oza, president of global business development at Ideal Cures. "With the advent of TA Associates coming on board, Ideal Cures aims to leverage TA's networking and other corporate development capabilities to accelerate growth in not only some of the fastest growing regions, like South Asia, but also in well-established markets around the world."

"We believe that the film coating industry is a unique, yet evolving sector that has strong potential for growth globally," said Naveen A. Wadhera, a managing director at TA Associates. "We expect that there are significant opportunities for expansion and are eager to help Ideal Cures further develop and enhance its brand and internal capabilities. We are delighted that Ideal Cures has chosen to partner with TA and look forward to helping them execute on their strategic vision."

Ideal Cures is a leading manufacturer and exporter of pharmaceutical excipients and ready-to-use coating systems for solid oral dosage forms. Through its network of customers and partners spanning across more than 40 countries, the company provides tailor-made solutions and products for the pharmaceutical, nutraceutical, herbal, and ayurvedic industries. Ideal Cures has EXCiPACT™ certified cGMP manufacturing plants located in Vasai, Jammu, and Khambat and R&D facilities in Mumbai and Vasai. The product portfolio comprises INSTACOAT® ready-to-use film coating systems, INSTANUTE® coating technology for nutraceuticals and dietary supplements, ECOPOL® range of pharma acrylic polymers, ECOCOOL® brand of cooling compounds, and ESPHERES® range of sugar, microcrystalline cellulose, silicon dioxide, calcium carbonate, and tartaric acid spheres. More information about Ideal Cures can be found at www.idealcures.com.

TA Associates is one of the largest and most experienced global growth private equity firms. The firm has invested in more than 480 companies around the world and has raised $24 billion in capital. With offices in Boston, Menlo Park, London, Mumbai, and Hong Kong, TA Associates leads buyouts and minority recapitalizations of profitable growth companies in the business services, consumer, financial services, healthcare and technology industries. More information about TA Associates can be found at www.ta.com.

Flowonix® Medical Inc. and Cerebral Therapeutics Announce World-First Clinical Trial Delivering Medication Directly into the Brain for Patients with Refractory Epilepsy

PRNewswire: March 14, 2017 – MOUNT OLIVE, NJ, U.S.A. – Flowonix Medical Inc. of New Jersey and Colorado-based Cerebral Therapeutics, announced today the first patients implanted with the Prometra® II programmable infusion system in the Australian Direct Drug Administration for Refractory Epilepsy (ADDRESS) clinical trial at St. Vincent's Hospital, Melbourne, Australia. The jointly developed therapy features a micro-infusion device that tightly controls drug delivery to a region of the brain for patients with medically refractory epilepsy.

ADDRESS is the first multi-center dose ranging clinical study assessing intracerebroventricular (ICV) delivery of the drug valproate (valproate sodium) in patients with focal seizures, with temporal lobe onset with or without secondary generalization. Nine patients will take part in this experimental treatment, wherein patients will receive ICV administration of valproate via the Flowonix Prometra II programmable pump. Clinicians associated with the trial are encouraged with the preliminary results in reducing the number of epileptic seizures.

"We are really excited to be able to study this new treatment option for patients in the ADDRESS trial—it may offer new hope to those with uncontrolled epilepsy," stated Prof. Mark Cook, chair of medicine and director of neurosciences at St. Vincent's Hospital in Melbourne, Australia.

Refractory epilepsy, referred to as uncontrolled, intractable, or drug-resistant epilepsy, occurs when medications do not bring seizures under control. Epilepsy patients that are refractory to oral anti-epileptic drug treatment have significantly higher mortality, higher morbidity, higher economic costs, and diminished quality of life compared to those who suffer from epilepsy that can be adequately controlled with medical management. About one in three people with epilepsy progress to refractory epilepsy.

"The ability to target-deliver anti-epilepsy medication through an established infusion pump delivery could be a treatment with profoundly positive ramifications," stated Dr, Ashwini Sharan, neurosurgical and neurological professor at Jefferson University, and president of the North American Neuromodulation Society. "This is the first time in the world this approach is being taken."

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Dan Abrams, chief executive officer of Denver-based Cerebral Therapeutics, noted that this is the first time implantable programmable pumps have been used to deliver medication directly to the brain, in the same way they are used to manage spinal pain by delivering medications to the intrathecal space.

According to the World Health Organization, nearly one person in six suffers from some type of neurological condition, amounting to over one billion individuals worldwide. Many neurological conditions can be addressed with medications, but there is still significant unmet medical need.

"Neurological disorders can be devastating to patients and their families, who are often left with few options," stated Larry Heaton, chief executive officer of Flowonix Medical, Inc. "Flowonix is emerging as a world leader in implantable drug infusion systems used to treat pain, and we have particular expertise in the accurate and reliable delivery of microdoses of medication."

He continued, "As the first trial of its kind, the ADDRESS study is a significant milestone for Flowonix Medical, Inc., Cerebral Therapeutics, the healthcare community, and patients worldwide. If the clinical study results in demonstrated positive outcomes, it would benefit patients who have refractory epilepsy and establish targeted drug delivery directly to the brain. It is gratifying when technological advancements offer such exciting possibilities for a new group of patients in need."

The Prometra programmable infusion system is FDA approved for intrathecal infusion of Infumorph® (preservative-free morphine sulfate sterile solution) or preservative-free sterile 0.9% saline solution (sodium chloride injection, USP). The Prometra II Pump is not approved for the ICV administration of valproate in the United States or Australia and is being studied as an investigational use only device in Australia.

Flowonix Medical Inc. (www.flowonix.com), headquartered in Mt. Olive, New Jersey, is working with healthcare professionals to help ease suffering associated with chronic pain, enabling patients to improve their lives through innovation and therapy advancements. Our goal is to become the leading implantable drug delivery company in the world. Founded in 2005, Flowonix is working closely with physicians to enhance the capabilities of implantable drug delivery systems. For more information, please visit www.flowonix.com.

Cerebral Therapeutics, LLC (www.cerebraltherapeutics.com) is a privately held company founded with the goal of addressing the well-recognized limitations of existing treatments for uncontrolled neurological diseases. Cerebral Therapeutics is combining advanced micro-dosing technology with proprietary medications to precisely deliver treatments to the other side of the blood-brain barrier to improve the lives of patients with uncontrolled neurological disease. With a promising route of administration, Cerebral Therapeutics offers a new approach to managing neurological diseases by means of delivering ideal dosing to targeted sites within the brain. Initially, Cerebral Therapeutics is focused on improving outcomes and propagation in the brain. Future cerebral therapeutic areas include obesity, Alzheimer's disease, Parkinson's disease, anxiety spectrum disorder, and brain cancer.

OncoSec Announces First Technology Access Program Agreement with Inhibrx

PRNewswire: March 14, 2017 – SAN DIEGO, CA, U.S.A. – OncoSec Medical Incorporated ("OncoSec") (NASDAQ: ONCS), a company developing DNA-based intratumoral cancer immunotherapies, announced today that they have entered into a technology access program (TAP) agreement with Inhibrx, LP, a privately held biotherapeutic company.

Under the agreement, Inhibrx will use OncoSec's proprietary gene delivery technologies, the GENESIS™ research generator and proprietary applicators, for preclinical discovery of antibodies.

"We initially announced the availability of the TAP in November, and I am excited to have Inhibrx signed on as the first company to use our devices for their internal research programs," said Punit Dhillon, OncoSec's chief executive officer. "We believe this program helps to facilitate discovery efforts for TAP partners while advancing OncoSec's proprietary technologies. By making our devices available for non-exclusive research use to both industry and academic collaborators, for a small licensing fee, we are building our internal data set around GENESIS™ while expending minimal internal resources."

"The ability of OncoSec's TRACE™ technology to optimize *in vivo* gene expression for animal immunization provides advantages over traditional antibody discovery approaches, especially for difficult to express and complex transmembrane proteins," said Mark Lappe, Inhibrx's chief executive officer. "We look forward to continuing to work with OncoSec through our TAP agreement to explore the use of *in vivo* electroporation for gene delivery and antibody discovery."

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The OncoSec GENESIS™ research generator was developed specifically for gene electro-transfer. It features customizable electroporation parameters for construct-specific optimization of expression, and it is the only *in vivo* electroporation device enabled with TRACE™ technology (tissue-based, real-time adaptive control electroporation). TRACE™ technology incorporates an electrochemical tissue-sensing control system to automatically adjust pulse width and treatment duration in real time during the electroporation procedure. This feature enables tissue- and therapeutic-specific delivery optimization, maximizing uptake of the therapeutic while reducing unnecessary cell ablation or damage. In research models, GENESIS™ with TRACE™ has yielded higher and more consistent *in vivo* protein expression versus fixed-parameter electroporation, even in heterogeneous tissues.

Potential advantages of using GENESIS™ with TRACE™ for the objectives of animal immunization include cost savings versus recombinant protein administration, a shortened pre-immunization timeline relative to recombinant protein production, and display of the immunizing antigen in its native conformation. The latter benefit may be particularly relevant for certain therapeutic indications, including immuno-oncology, in which many key targets require functional agonism and/or structurally complex therapeutic modalities such as multimeric forms. To date, OncoSec has generated multiple high-titer antibody libraries against immuno-therapeutic targets.

The OncoSec technology access program makes OncoSec's electroporation technologies available to collaborators for preclinical research. Devices are available for intratumoral, intradermal, and intramuscular delivery. For more information, please contact bd@oncosec.com.

OncoSec is a biotechnology company developing DNA-based intratumoral immunotherapies with an investigational technology, ImmunoPulse®, for the treatment of cancer. ImmunoPulse® is designed to enhance the local delivery and uptake of DNA-based immune-targeting agents, such as IL-12. In phase I and II clinical trials, ImmunoPulse® IL-12 has demonstrated a favorable safety profile and evidence of anti-tumor activity in the treatment of various solid tumors as well as a systemic immune response. OncoSec's lead program, ImmunoPulse® IL-12, is currently in clinical development for metastatic melanoma and triple-negative breast cancer. The program's current focus is on the significant unmet medical need in patients with melanoma who are refractory or non-responsive to anti-PD-1/PD-L1 therapies. In addition to ImmunoPulse® IL-12, the company is also identifying and developing new immune-targeting agents for use with the ImmunoPulse® platform. For more information, please visit www.oncosec.com.

Inhibrx is a clinical stage biologic immunotherapeutic company focused on the treatment of high unmet medical needs in oncology, infectious disease, and inflammatory conditions. Inhibrx's proprietary platforms enable fit-for-function biotherapeutics that optimally interface with the biology of each target antigen to focus and conditionally modulate immune activities and mediate enhanced signaling. Therapeutic proteins include multispecific and multivalent molecules designed and crafted using our composite modular single domain antibody technology. For more information, visit www.inhibrx.com.

Bonesupport™ Extends U.S. Distribution Agreement for Cerament™|Bone Void Filler

PRNewswire: March 14, 2017 – LUND, Sweden – Bonesupport AB, an emerging leader in innovative injectable bioceramic bone scaffolds to treat bone voids caused by trauma, infection, disease, or related surgery, announces that it has extended the term of its U.S. distribution agreement with Zimmer Biomet. Under the agreement, Zimmer Biomet will continue to have exclusive rights for Bonesupport's proprietary Cerament bone void filler product line for orthopedics, trauma, and foot and ankle indications in the United States.

"We are extremely pleased to extend our distribution agreement with Zimmer Biomet," said Richard Davies, CEO of Bonesupport™. "The partnership has been very successful and has resulted in the current rapid growth of our flagship product, Cerament, in the world's largest bone graft substitute market. This rapid growth is building an important platform from which we can launch product extensions into the United States."

In addition to commercialization of Cerament bone void filler in the U.S. market, Bonesupport is currently enrolling patients into the FORTIFY clinical study, an FDA-approved IDE randomized control pivotal study for the company's anti-biotic eluting product Cerament G. Cerament G is currently approved and commercialized in the European Union and other markets outside the United States.

Bonesupport has developed Cerament as an innovative range of radiopaque injectable osteoconductive bioceramic products that have a proven ability to heal defects by remodeling to host bone in six to 12 months. Our products are effective in treating patients with fractures and bone voids caused by trauma, infection, disease, or related surgery. Our lead product, Cerament bone void filler (BVF) addresses important issues facing health care providers, such as avoiding hospital readmissions and revision surgery that result from failed bone healing and infection caused by residual bone voids. Cerament BVF is commercially available in the United States, European Union, Southeast Asia, and the Middle East.

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Cerament's distinctive properties as a drug eluting material have been validated in clinical practice by Cerament G and Cerament V, the first CE-marked injectable antibiotic eluting bone graft substitutes. These products provide local sustained delivery of gentamicin and vancomycin, respectively. The local delivery feature enables an initial high concentration of antibiotics to the bone defect and then a longer sustainable dose above the minimal inhibitory concentration (MIC) to protect bone healing and promote bone remodeling.

Cerament G and Cerament V have demonstrated good results in patients with problematic bone infections including osteomyelitis. They are also used prophylactically in patients who are at risk for developing infection. Cerament G and Cerament V are available in the European Union.

Bonesupport was founded in 1999 by Prof. Lars Lidgren, an internationally respected scientist who has been the president of various musculoskeletal societies. Bonesupport's mission is to improve the lives of patients suffering from bone disorders that cause bone voids, lead to injury, breakage, pain, and reduced quality of life. The company is based in Lund, Sweden. www.bonesupport.com

Texas A&M University Joins NIPTE as Its 17th Member Institution

Business Wire: March 10, 2017 – MINNEAPOLIS, MN, U.S.A. – The National Institute for Pharmaceutical Technology and Education (NIPTE) welcomes Texas A&M Irma Lerma Rangel College of Pharmacy to the organization as its 17th member. Indra K. Reddy, PhD, the college's founding dean, will serve on the NIPTE board of directors. As a NIPTE member, Texas A&M will contribute to its various scientific and educational programs.

"Texas A&M's infrastructure and expertise in drug delivery, formulations design (including pediatric and abuse deterrent formulations), manufacturing, and regulatory science for complex products are among the best in the nation," said Vadim J. Gurvich, PhD, MBA, NIPTE's executive director and research associate professor at the University of Minnesota. "These competencies align well with our priorities—and our stakeholders'—adding to the critical mass we are establishing to offer programs and solutions that are urgently needed by the nation's pharmaceutical quality system."

"Texas A&M is delighted to join the outstanding group of NIPTE institutions with a common mission to improve human health through multi-university, collaborative research," Reddy said. "At a time when FDA regulations and the pharma industry are poised to change dramatically, it is imperative that our complex products that are being developed and policies that are in effect to regulate these products in the nation are science-based with transparency for best quality assurance. NIPTE has done a commendable job of recognizing these needs and bringing together the best and brightest of pharmaceutical scientists, engineers, and chemists to solve global challenges. We look forward to working and advancing human health with our NIPTE colleagues."

NIPTE is a 501(c)(3) nonprofit academic organization dedicated to excellence in fundamental research and education in pharmaceutical science and manufacturing. Its mission is to improve human health through multi-university collaborative research by advancing quality, safety, affordability, and speed to market of medicines. NIPTE is comprised of 17 top U.S. schools of pharmacy, chemical and pharmaceutical engineering, and a medical school. Current members are Duquesne University, Illinois Institute of Technology, Long Island University, Purdue University, Rutgers University, Texas A&M University, University of Connecticut, University of Iowa, University of Kansas, University of Kentucky, University of Maryland Baltimore, University of Michigan, University of Minnesota, University of Puerto Rico, University of Rochester Medical Center, University of Texas, and University of Wisconsin.

BioPact's MGMR® Drug Delivery Technology Succeeds in Transporting Cell Impermeable Peptides Across Cell Membrane Triggering 100% Cancer Cell Death

PRNewswire: March 9, 2017 – AUSTIN, TX, U.S.A. – BioPact's nanodelivery technology, MGMR®, demonstrated highly efficacious intracellular delivery of KLAKLAK, a pro-apoptotic peptide known to be cell membrane impermeable. When loaded on MGMR, KLAKLAK crossed the cell membrane of LNCaP human prostate cancer cells, triggering apoptosis in 100% of the cells in repeated studies.

KLAKLAK is a 1.5kD peptide with pro-apoptotic properties. MGMR binds to KLAKLAK with a high affinity and transports the peptide across the cell membrane without the need for targeting moieties to aid or enable the transport. MGMR, alone, is well tolerated by cells and, as expected, did not trigger cell death. KLAKLAK alone is unable to cross the cell membrane, and cells are unaffected by its presence outside the cell. Only when combined were MGMR and KLAKLAK able to elicit an apoptotic effect on the cells, quantified by DAPI stain. The results were verified by repeated tests which confirm the apoptosis-inducing nature of the MGMR/KLAKLAK construct. MGMR has already demonstrated in other studies an ability to penetrate other cell types. MGMR brings superiority over other forms of cell transport delivery systems in that it has high loading efficiency (high therapeutic quantities

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to MGMR ratio), lacks the need for permeation moieties, can be used in a wide variety of cell types, and is able to scale manufacturing at an economical cost.

BioPact's chief executive officer, Joe Dillon, Ph.D., MBA, commented, "This was a bellwether study for BioPact and an exciting beginning of further studies we are conducting to deliver difficult to target therapies." Lainie Mulvanny, VP of business development, noted, "Practical intracellular delivery is clearly an unmet need in the drug delivery space. We are looking forward to discussing this data with our potential collaborative partners at BIO-Europe Spring this month."

The ability to target intracellular peptides is a challenge in drug delivery. MGMR has demonstrated this successfully, and BioPact will apply this method of transportation to other areas of therapeutic delivery. BioPact plans to produce multiple data sets in regards to cell penetration data with siRNA, proteins, blood-brain barrier passage with molecules, and gut survivability with active API in the first half of 2017.

BioPact is a medical nanotechnology development company. Our drug delivery platform is a unique composition of matter derived from carbon nanotubes called Medical Grade MOLECULAR REBAR®, or MGMR. By utilizing MGMR, drug developers can address challenges in many arenas such as controlled release, targeted delivery, transdermal delivery, toxicity or instability challenges, intracellular delivery, and crossing the blood-brain barrier. MGMR are discrete (individual), safe, free of impurities, open-ended, length controlled, and surface functionalized carbon nanotubes. The unique physical properties of these tubes overcome the limitations of traditional CNTs, which are impure, tangled carbon bundles. MGMR can be loaded internally with large and/or small molecules regardless of hydrophobicity and large and/or small molecules can be bonded to the exterior of the tube with multiple surface functionalities to optimize the molecule bond. For additional company information, visit www.bio-pact.com.

PolyPid Announces Positive Interim Data from Company's Confirmatory Clinical Trial for BonyPid®-1000 Antibiotic Eluting Bone Substitute

PRNewswire: March 9, 2017 – PETAH TIKVA, Israel – PolyPid Ltd., an emerging clinical-stage specialty pharmaceutical company focused primarily on the development of post-surgical anti-infective pipeline, announced today interim results from the first group of patients having reached the six-month follow-up period in the company's confirmatory clinical trial of BonyPid®-1000, a doxycycline-eluting synthetic bone substitute (β tri-calcium phosphate [β TCP] granules).

The BonyPid®-1000-103 trial is a randomized, single-blind standard of care controlled study in a total of 64 patients with open tibia fractures (Gustilo IIIA and IIIB), a severe clinical condition resulting from a high energy traumatic event where the bone is severely damaged and exposed and, therefore, assumed to be contaminated by environmental bacteria. This multi-center study is being conducted at six clinical sites in Israel and three in Asia. The objective of the study is to determine performance and safety of standard of care (SOC) plus BonyPid®-1000 on bone healing in traumatic open fracture patients over a period of six and 12 months, compared with SOC alone. The primary performance endpoint is radiographic-assessed bone healing during the 24-week follow-up period, based on independent blinded central radiographic evaluations of the target fracture's X-rays.

Based on the interim results from the first group of patients to reach the 16-week follow-up period, 12 patients treated with standard of care SOC plus BonyPid®-1000 versus 13 patients treated with SOC alone, time from surgery to the initiation of bone healing as assessed by the treated physicians (callus in one out of four cortices) was reduced by approximately 33% in the BonyPid®-1000 plus SOC treated group (95% confidence interval for 75% of the patients). Moreover, solid radiographic markers for bone healing (callus in three of four cortices), the study's primary performance endpoint, was reduced by 32%, 75 days in patients treated with BonyPid®-1000 plus SOC, versus 110 days in patients receiving SOC alone (95% confidence interval for 50% of the patients). In addition, at 16 weeks' time, more than 30% of the patients treated with SOC did not achieve the primary performance endpoint, versus 8% of the patients treated with SOC plus BonyPid®-1000. These results are consistent with the evaluation from the independent radiographic, where time to the initiation of solid bone healing (callus in three out of four cortices) was reduced by 28%, 82 days in patients treated with BonyPid®-1000 plus SOC, versus 114 days in patients receiving SOC alone (95% confidence interval for 50% of the patients). In addition, pain-free weight bearing was demonstrated in 63% of the patients receiving BonyPid®-1000 plus SOC four months post-surgery, versus none of the patients (0%) receiving SOC alone.

"We are extremely pleased with these interim data," said Amir Weisberg, PolyPid's chief executive officer. "These compelling results further expand the growing body of clinical evidence highlighting the effectiveness of our BonyPid®-1000 in promoting bone healing and its potential in reducing the economic burden caused by prolonged recovery times. A significant unmet medical need exists for patients suffering from severe open fractures in order to reduce surgical interventions and bone healing time. Based on the data generated to date, we believe BonyPid®-1000 has the potential to address this treatment void, and we look forward to continuing our BonyPid®-1000-103 study."

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As in previous clinical studies, there were no product-related adverse events reported in the patients receiving BonyPid®-1000 plus SOC. PolyPid anticipates enrolling the last patient into the study by year-end 2017.

BonyPid®-1000 is a bone graft substitute eluting doxycycline hyclate, a broad-spectrum antibiotic. The antibiotic is released locally over a prolonged period of four weeks by the PLEX™ technology. BonyPid®-1000 has successfully completed multiple pilot clinical trials in the severe open fracture indication, demonstrating excellent safety and efficacy results, including 0% infections in the target fracture, and 0% amputations after six to 12 months of follow-up (vs. an average of 25 and 7%, respectively, in a historical control group of patients).

PolyPid is a clinical stage, emerging specialty pharmaceutical company developing, manufacturing, and commercializing products based on a proprietary platform, PLEX™ (Polymer-Lipid Encapsulation matriX), in the field of extended release, local drug delivery. PLEX™ technology optimizes drug therapeutic performance and clinical outcomes, improves pharmacoeconomic potential, and offers lifecycle extension for novel drugs. This is achieved via protected drug reservoirs enabling prolonged delivery of drugs, including biologics, over periods ranging from days to several months. The application of PLEX™ technology enables optimized drug treatment regimens by predetermining release rates and durations, a rare combination of attributes. PLEX™-based products have demonstrated an excellent safety profile during extended clinical studies, with over 65 patients exposed to the technology to date. PolyPid's technology and products are based on the inventions of Dr. Noam Emanuel, the founder and the chief technology officer of the company.

PolyPid's lead product, D-PLEX™, is a secure antibiotic drug reservoir that provides a safe and effective local anti-bacterial preventive and eradication treatment at the target site and is designed to be administered during surgical procedures. After surgery, the drug reservoir constantly releases the entrapped antibiotic over several weeks, thus allowing prolonged infection management with increased potential to eradicate antibiotic resistant bacteria. For additional company information, visit www.polypid.com.

Vaxess Technologies Receives Grants Totaling $6 Million to Develop Microneedle Vaccines for Polio, Measles, and Rubella

PRNewswire: March 6, 2017 – BOSTON, MA, U.S.A. – Vaxess Technologies, Inc., an innovative life sciences company developing novel vaccine stabilization and delivery technologies, received two grants from the Bill & Melinda Gates Foundation to advance the development of inactivated polio (IPV) and live attenuated measles rubella (MR) vaccines using the company's MIMIX™ sustained-release microneedle patch platform.

"Vaxess has teamed up with the Bill & Melinda Gates Foundation to develop an innovative technology that will contribute to eradication of polio and prevention of measles and rubella by increasing vaccine access," said Vaxess vice president Livio Valenti. "Products developed with our MIMIX™ sustained-release vaccine delivery system will have increased product efficacy and will not require refrigeration, facilitating vaccination in resource-poor settings."

MIMIX™ is Vaxess's proprietary technology platform for sustained transdermal delivery of vaccines and immunotherapies. Products made with MIMIX™ technology can be administered using a resorbable patch that delivers the vaccine by application to the skin as opposed to the traditional needle-and-syringe approach. By engineering biopolymer microneedles to encapsulate antigens for transdermal administration and controlled release, the goal of MIMIX™ is to enable vaccine products with greater efficacy, simplified dosing and administration, and enhanced stability under ambient or harsh environmental conditions.

The first grant from the Gates Foundation of roughly $3 million represents phase I of a multi-stage grand challenges grant to support the development of Vaxess's innovative technologies for the manufacture of microneedle patch vaccines. In this phase, the grant will support Vaxess's preclinical development and manufacture of a thermostable IPV microneedle patch with the aim of lowering barriers to vaccine access by simplifying dosing and administration, alleviating cold chain constraints, and lowering costs.

"The use of the MIMIX sustained-release microneedle patch to combine doses and simplify administration has the potential to streamline global eradication efforts," said Vaxess CEO Michael Schrader. "Vaxess is honored to work with the Bill & Melinda Gates Foundation to advance these life-saving products to market."

The second grant of roughly $3 million will support the preclinical development of a resorbable microneedle patch for delivery of live attenuated MR vaccine. Under the grant objectives, Vaxess will develop a thermostable MR vaccine formulation, fabricate microneedle patches incorporating the stable formulation, and establish preclinical proof-of-concept in appropriate animal models to support clinical trials in a later stage of development.

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"Vaxess's MIMIX platform, enabled by the unique properties of silk-derived biopolymers, offers tunable dermal delivery of antigens to optimize immune response and improve product profiles," said Vaxess vice president of R&D Kathryn Kosuda, PhD. "With support from the Bill & Melinda Gates Foundation, we are excited to demonstrate the flexibility and power of this platform to advance IPV and MR vaccines."

Vaxess Technologies, Inc, is a life sciences company based in Boston, Massachusetts. Vaxess is commercializing the MIMIX™ microneedle platform for sustained transdermal delivery of vaccines and therapies and the MATRIX formulation and drying platform for the development of thermostable vaccine, therapeutic, and diagnostic products. For more information, please visit Vaxess's website at www.vaxess.com or send additional inquiries to contact@vaxess.com.

February

Intersect ENT Announces FDA Approval of Newest Steroid Releasing Implant, PROPEL® Contour, for Use in Treating the Frontal and Maxillary Sinuses

Business Wire: February 24, 2017 – MENLO PARK, CA, U.S.A. – Intersect ENT, Inc. (Nasdaq: XENT), a company dedicated to transforming care for patients with ear, nose, and throat conditions, today announced that the company has received approval from the U.S. Food and Drug Administration (FDA) for its PROPEL® Contour steroid-releasing sinus implant. PROPEL Contour features an innovative hourglass design that facilitates treatment of patients with chronic sinusitis in the frontal (behind the forehead) and maxillary (behind the cheeks) sinuses.

With this approval, Intersect ENT's PROPEL family of steroid-releasing implants allows for treatment of patients undergoing ethmoid, frontal, or maxillary surgeries, which represent the majority of procedures for the treatment of chronic sinusitis.

PROPEL Contour, the latest in the PROPEL family of steroid-releasing sinus implants, is specifically designed to conform to the sinus ostia (openings), focusing drug delivery and mechanical support where it is needed in order to maximize sinus surgery outcomes. The implant features a low-profile flexible delivery system to make it easier to access tight areas of the sinus anatomy.

"The approval of PROPEL Contour adds a third product under the PROPEL umbrella, expanding our offering of steroid-releasing implants to improve surgical outcomes," said Lisa Earnhardt, president and CEO of Intersect ENT. "With its strong clinical evidence, we expect that PROPEL Contour will extend adoption of our sinus implants both in the operating room as well as in the office, and that offering physicians a wide range of products to customize treatment based on their patients' disease and anatomy will ultimately lead to broader overall usage."

Positive data from the PROPEL Contour cohort of the PROGRESS study, a prospective, randomized, blinded, multi-center trial of 80 patients designed to assess the safety and efficacy of the implant when placed in the frontal sinuses following surgery, supported the approval. The study met its primary efficacy endpoint, demonstrating a statistically significant 65% relative reduction in the need for post-operative interventions, such as the need for additional surgical procedures or the need for oral steroid prescription, compared to surgery alone.

"The introduction of PROPEL steroid-releasing implants has led to meaningful benefits in how we as surgeons manage our patients, especially by reducing our reliance on oral steroids to prevent post-operative complications," said Robert Weiss, M.D., director and founder of CT ENT Sinus and Allergy Hearing and Balance in Norwalk, Connecticut, and one of the PROGRESS study investigators. "With PROPEL Contour, we are able to offer those benefits to a significant range of our chronic sinusitis patients, regardless of their unique anatomy, and to do so with the comfort of the same rigorous clinical evidence for which the PROPEL family of products is known. With this base of solid evidence pointing to a clear benefit, there are strong reasons to include PROPEL as part of standard clinical practice."

Intersect ENT's PROPEL products are the first and only dissolvable steroid-releasing sinus implants approved by the FDA. Clinically proven to improve outcomes for chronic sinusitis patients following sinus surgery, PROPEL sinus implants mechanically prop open the sinuses and release mometasone furoate, an advanced corticosteroid with anti-inflammatory properties, directly into the sinus lining then dissolve. PROPEL's safety and effectiveness are supported by level 1-A clinical evidence from multiple clinical trials, which demonstrates that PROPEL implants reduce inflammation and scarring after surgery, thereby lessening the need for post-operative oral steroids and repeat surgical interventions. More than 150,000 patients have been treated with PROPEL products to date. PROPEL is indicated for the ethmoid sinus; PROPEL Mini is indicted for the ethmoid and frontal sinuses; and PROPEL Contour is indicated for the frontal and maxillary sinuses.

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PROPEL Contour represents the newest addition to the PROPEL family of dissolvable steroid-releasing implants, clinically proven to improve results of sinus surgery. With its unique hourglass shape, PROPEL Contour conforms to sinus ostia, propping sinuses open while delivering anti-inflammatory medication when placed in the operating room or sinus dilation in the physician's office. PROPEL Contour's low-profile design allows for placement in smaller sinus openings, like those of the frontal and maxillary sinuses, expanding the applicable patient population for steroid-releasing implants.

Intersect ENT is dedicated to transforming the landscape of care for patients with ear, nose, and throat conditions. The company's PROPEL® family of dissolvable steroid-releasing sinus implants are clinically proven to improve outcomes for chronic sinusitis patients undergoing sinus surgery. In addition, Intersect ENT is continuing to expand its portfolio of products based on the company's unique localized steroid-releasing technology and is committed to broadening patient access to less invasive and more cost effective care. For additional information on the company or the products including risks and benefits, please visit www.IntersectENT.com.

CTT Pharmaceutical Holdings and CanniMed Therapeutics Inc. Complete Exclusive Canadian Licensing Agreement for Cannabis Orally Dissolvable Thin Film (ODF) Wafer

Business Wire: February 17, 2017 – SASKATOON, SK, and STONEY CREEK, ON, Canada – Today, CanniMed Therapeutics Inc. (TSX: CMED) and CTT Pharmaceutical Holdings Inc. (OTCQB: CTTH) have entered into a definitive contractual relationship for the licensing of CTT's orally dissolvable thin film (ODF) wafer technology.

This industry-first collaboration includes the licensing of six patents related to cannabinoid and opioid delivery for pain management, which will enable CMED to exclusively develop and commercialize this novel, smoke-free drug delivery system in Canada.

"The CanniMed ODF wafers will complement the already well-integrated line of CanniMed® oil products we have in market, broadening our ability to provide patients with standardized, dose-sensitive, and discreet delivery systems," said Brent Zettl, president and CEO, CanniMed Therapeutics Inc. "Collaborations with innovative companies such as CTT Pharma, and continued research and development into products that will further position medical cannabis as an important therapeutic option is a core focus of our company."

Orally dissolvable thin film (ODF) wafers are a proprietary drug delivery mechanism in the form of paper-thin polymer films used as carriers for pharmaceutical agents, with the following benefits:

- ODF wafer is taken orally but does not require water or swallowing.
- ODF wafers dissolve quickly in the oral cavity (5–15 seconds) with the active ingredient rapidly absorbed and diffused into the dense network of capillaries for direct access to the bloodstream via the oral mucosa.
- The active ingredient, once absorbed, bypasses the liver's first-pass effect, improving therapeutic outcomes and efficacy through improved bioavailability and facilitating excellent patient compliance.
- ODF wafer is suitable for a wide range of patients, including for geriatric and pediatric patients who experience difficulty swallowing or patients who suffer from phagophobia (fear of swallowing) or pnigophobia (fear of choking).

"We are excited to announce the completion of our agreement with CanniMed Therapeutics; this is an excellent opportunity for us to marry our novel and patented delivery technology to CanniMed's industry leading presence in the medical cannabis sector," said Dr. Pankaj Modi, president and CEO, CTT Pharmaceutical Holdings. "We look forward to offering CanniMed's existing patient population our convenient, smoke-free drug delivery system, which will help patients to take precise and accurate doses of cannabinoids as prescribed for pain management, mental disorders like depression, anxiety, post-traumatic stress disorder, and a reduction in epileptic seizure syndromes in children. As the industry continues to grow and evolve we feel that we have chosen the right partner to introduce our product, tailor it to specific indications, and to scale throughout Canada."

CTT's principal asset is a unique and novel patented drug delivery technology, an orally administered, fast dissolving thin film (the "wafer"). This technology platform will target both the human and veterinarian (pet) markets for treatment of many diseases including pain management.

The oral thin film (wafer) formulation is protected by several Canadian and U.S. patents. CTT's oral fast dissolving drug delivery systems will consist of edible thin films (wafers) that dissolve without water, within a few seconds after placement in the mouth. The majority of drugs administered using our drug delivery system mirror injections in that they have the ability to enter the bloodstream quickly, are convenient and discreet, and can be administered anywhere. A faster absorption rate is achieved because the mouth

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contains a very thin mucosa and is extremely vascular. There is no bitter taste, no smoke inhalation as is the case with cannabis, and less degradation of medication (by bypassing the stomach), and most importantly lower dosage units are required given the efficacy of absorption. Patient compliance is improved, especially with those who have a fear of choking and/or are pediatric, geriatric, or incapacitated patients who have difficulty swallowing.

Most fast dissolving systems on the market today deliver anti-inflammatories, antihistamines, and cough and breathing related medications. CTT believes that its wafer technology will be one of the first to gain use in major markets such as pain management. For more information, please visit www.cttpharmaceuticals.com.

The company is a Canadian-based, international plant biopharmaceutical company and a leader in the Canadian medical cannabis industry, with 15 years of pharmaceutical cannabis cultivation experience, state-of-the-art, GMP-compliant plant production processes, and world-class research and development platforms with a wide range of pharmaceutical-grade cannabis products. In addition, the company has an active plant biotechnology research and product development program focused on the production of plant-based materials for pharmaceutical, agricultural, and environmental applications.

CanniMed Ltd., a wholly owned subsidiary of the company, was the first producer to be licensed under the Marihuana for Medical Purposes Regulations, the predecessor to the current Access to Cannabis for Medical Purposes Regulations.

Prairie Plant Systems Inc., a wholly owned subsidiary of the company, was the sole supplier to Health Canada under the former medical marijuana system for 13 years, and has been producing safe and consistent medical marijuana for thousands of Canadian patients, with no incident of diversion. For more information, please visit our websites: www.cannimed.ca (patients) and www.CanniMedTherapeutics.com (investors).

Ferring and Foresee Pharmaceuticals Enter into Exclusive Development and Option Agreement

Business Wire: February 13, 2017 – SAINT-PREX, Switzerland – Ferring Pharmaceuticals and Foresee Pharmaceuticals Co., Ltd. (6576.TWO), announced today that the companies have entered into an exclusive worldwide development and option agreement to leverage Foresee's proprietary and unique stabilized injectable formulation platform (SIF) for the development of long duration, controlled release formulations of a peptide therapeutic.

Under the terms of the agreement, Ferring will fund the development work and, upon completion, Ferring will have the right to exercise its option and enter into a definitive agreement with Foresee. Execution of a definitive agreement would entitle Foresee to additional payments including upfront, milestones, and royalties based on net sales of the product(s) commercialized by Ferring.

"We have been impressed with Foresee's achievements to date, and we see value in its SIF platform technology," said Alan S. Harris, senior vice president, R&D executive office at Ferring. "The technical barriers Foresee has overcome in developing stable, formulated peptides in solution for controlled release therapy for three and six month durations of action after a single injection are quite significant, and this gives us much confidence in the potential of the SIF platform applied to complex peptide drug substances. We are enthusiastic about this new collaboration."

"We are excited about entering into this collaboration with Ferring, a global specialty pharmaceutical company with a long-standing history of innovation in the area of injectable therapeutic peptides and the application of novel formulations and delivery technologies to generate differentiated product profiles," said Dr. Ben Chien, chairman and CEO of Foresee. "We are confident that our SIF platform will provide significant value to Ferring's R&D product portfolio and very much look forward to working with them on this project."

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

Foresee is a Taiwan and U.S.-based biopharmaceutical company listed on the Taipei Exchange. Foresee's R&D efforts are focused in two key areas, namely its unique stabilized injectable formulation (SIF) depot delivery platform and derived drug products targeting large specialty markets, and its transformative early stage preclinical and clinical NCE programs targeting inflammatory and fibrotic diseases and other disease areas with high unmet needs. Foresee has a product portfolio including late stage and early stage programs such as FP-001, a stable, premixed, prefilled version of leuprolide depot for injection, which has recently successfully completed a

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global phase III registration study, and FP-025, a highly selective oral MMP-12 inhibitor targeting inflammatory and fibrotic diseases, which is currently completing a phase 1 study.

Nemaura Pharma Secures Funding to Advance Its Micro-Patch™ Solid Dose Microneedle System for a Hormone Biologic

Business Wire: February 7, 2017 – LOUGHBOROUGH, England – U.K. biotech company Nemaura Pharma has announced a commitment from private investors of up to £5 million for the development of a hormone biologic using its Micro-Patch™ solid dose delivery platform. The fast-growing company has made significant progress in the reformulation of liquid vaccines administered through the skin using its solid dose delivery system. The funding is being used to accelerate Nemaura's commercial research and development of clinical programmes to prepare the drug-device combination for market.

According to global growth strategy analyst Frost & Sullivan, Nemaura's drug delivery technologies have the potential to revolutionise the way drugs are delivered in the healthcare system. The company's solid dose delivery device, the Micro-Patch™, was cited in the 2016 Frost & Sullivan award for best practices in enabling technology leadership in the transdermal drug delivery industry. The Micro-Patch™ works by depositing the drug under the outer layer of the skin using a metal needle that then retracts completely, minimising the risk of stick injuries. The solid dose delivery device, which has been designed for safe patient self-administration, has the potential to improve control over drug release and absorption, improve stability performance, and either partially or completely eliminate the cold storage requirements for vaccines and biologics.

CEO Dr. Faz Chowdhury says, "Our advanced delivery technologies are designed to transform the way therapeutic drugs are administered through the skin, and this is an exciting time for the company and its collaborators. We know that conventional liquid formulations of vaccines and biologics carry stability risks, especially if they aren't stored at the correct temperature; this is costly, potentially dangerous, and a major issue for developing countries. In solid form, the drug can remain stable for several months without loss of potency. That's why we are eager to extend our biologics and vaccines reformulation activity by working with the right partners to help us take our research forward."

The maintenance of a temperature-controlled supply chain represents a major cost in the administration of vaccines and biologics overall, and its elimination would lead to significant savings. Data analysed by *Pharmaceutical Commerce* magazine estimate the 2017 global logistics costs of handling cold chain products in the pharmaceutical industry will be around $7.5 billion.

The Frost & Sullivan recognition of Nemaura's advanced technology capability comes ahead of anticipated company growth this year. The value of the global skin drug delivery market is expected to reach £33 billion by 2018, and the company aims to be one of the leading pharmaceutical technologists in this market. Founded in 2005, Nemaura has patents secured or pending across multiple patent families and now employs over 25 medical device technologists and bioscientists based on the Loughborough University Science and Enterprise Park.

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

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

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

Already one of the United Kingdom's largest science and enterprise parks, Loughborough University Science and Enterprise Park (LUSEP) combines a purpose-built corporate environment with a complementary R&D base and skilled workforce supply, made possible by its location on the university campus. Nemaura Pharma is one of around 50 high-tech companies based in the Science and Enterprise Park that benefit from close proximity to the M1 motorway and international connections through Birmingham and East Midlands airports. www.lusep.co.uk.

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January

Noveome Biotherapeutics, Inc., Publishes Data Demonstrating Anti-Inflammatory Activity of ST266 in a Preclinical Model of Optic Neuritis

Business Wire: January 31, 2017 – PITTSBURGH, PA, U.S.A. – Noveome Biotherapeutics, Inc., a clinical-stage company and leader in the field of paracrine signaling, today announced the publication of groundbreaking preclinical data in a multiple sclerosis (MS) model with ST266, the company's novel secretome. Intranasally delivered ST266 demonstrated anti-inflammatory activity and prevented retinal ganglion cell (RGC) loss in the optic nerve, showing its therapeutic potential for treating optic neuritis, the most common presenting sign of MS. The research was conducted in the laboratory of Kenneth S. Shindler, M.D., Ph.D., a professor of ophthalmology in the Perelman School of Medicine at the University of Pennsylvania, with funding support provided by Noveome, and was published today in *Nature Scientific Reports* in an article titled "Intranasal Delivery of a Novel Amnion Cell Secretome Prevents Neuronal Damage and Preserves Function in a Mouse Multiple Sclerosis Model."

Results showed that intranasally administered ST266 in a preclinical model reached the central nervous system within 30 minutes and was detected at higher concentrations in the vitreous and optic nerve than the brain, demonstrating that intranasal delivery can target tissues of the eye. In a preclinical model of optic neuritis, early treatment with ST266 prevented neuronal damage and dysfunction by significantly reducing the loss of RGCs, suppressing inflammatory cell infiltration into the optic nerve, and limiting the degree of demyelination induced by optic neuritis. Treatment of later-stage optic neuritis showed similar results, with ST266 administration leading to a reduction in neuronal damage and demyelination, resulting in improved visual function compared to untreated groups. These data suggest that ST266 helps promote RGC survival by potentially activating multiple pathways, including the stimulation of SIRT1-mediated mitochondrial function and AKT phosphorylation to prevent cell death. Intranasal drug delivery is not currently used to treat any ophthalmic conditions, including optic nerve diseases, and the current results support further exploration of this novel treatment strategy.

"Current therapies reduce inflammation but fail to prevent RGC loss; thus, there is a need for combination treatment options that are able to prevent RGC axon loss for patients with optic neuritis. The unique and diverse biologic molecules present in ST266 were seen to help promote anti-inflammatory and neuroprotective activity in this preclinical model and suggest that ST266 has the potential to mediate neuroprotection through activation of multiple intracellular signaling pathways," said Dr. Shindler. "These results are particularly important as the preservation of RGCs has been recognized as a significant factor when treating optic neuritis due to potential permanent visual dysfunction."

"We believe this is the first demonstration of a potentially successful therapeutic treatment of the optic nerve using intranasal delivery of large molecular weight biomolecules," commented Larry Brown, Sc.D., chief scientific officer of Noveome. "These promising results reinforce the multifaceted potential of ST266 in multiple disease areas, including disorders in the back of the eye. The study also reconfirmed the safety profile and potent nature of ST266 in a preclinical model, which provides encouragement and support for continued research."

ST266 is a novel secretome—a rich, complex solution of biologically active molecules secreted from proprietary cells. Instead of a single drug and target, the ST266 secretome utilizes paracrine signaling to induce changes in nearby cells, including modulating inflammation, speeding impaired wound healing, promoting bone restoration, restoring nerve function, regenerating cells, and restoring cellular homeostasis. ST266 has demonstrated these unique attributes in multiple preclinical studies, indicating that it can be applied across a wide range of disease indications to improve patient outcomes. In addition, phase I clinical trials have demonstrated the robust safety of ST266 when administered in ophthalmic, dermal, and oral formulations.

Noveome is a Pittsburgh, Pennsylvania-based, clinical-stage biotherapeutics company leveraging the science of paracrine signaling to restore cellular communication in impaired tissue and disease processes. Our paracrine therapeutic approach has the potential to create safe and effective products across a wide range of disease indications to improve patient outcomes. For more information on Noveome, visit www.noveome.com.

Ferring Pharmaceuticals and Enteris BioPharma Enter License Agreement to Develop an Oral Formulation of a Peptide-Based Injectable Therapeutic

Business Wire: January 30, 2017 – SAINT-PREX, Switzerland – Ferring Pharmaceuticals and Enteris BioPharma, Inc., announced today that the companies have entered into a license agreement and initiated an early development agreement to leverage Enteris's proprietary and patented oral peptide and small molecule delivery platform, Peptelligence™, to engineer an oral formulation of a peptide-based injectable therapeutic developed by Ferring.

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Under the terms of the agreement, Enteris BioPharma will license to Ferring its oral drug delivery technologies, as well as provide clinical trial finished product, and will receive milestones and royalties based on net sales of the developed product.

The licensing agreement with Ferring Pharmaceuticals highlights Enteris BioPharma's successful "feasibility-to-licensing" strategy involving Peptelligence™, its peptide and small molecule oral drug delivery platform. The technology is currently the subject of several active external development programs and has proven effective over the last decade to enable the safe delivery of peptide-based therapeutics and other molecules with low oral bioavailability.

Joel Tune, chief executive officer and executive chairman of Enteris BioPharma, remarked, "Our agreement with Ferring Pharmaceuticals exemplifies the opportunity our Peptelligence platform offers in enhancing the market potential of peptide-based therapeutics by enabling the oral delivery of medications that must otherwise be administered by injection. We are excited to work with an industry leader like Ferring Pharmaceuticals to advance the development of an oral peptide-based therapeutic."

Alan Harris, senior vice president, R&D executive office of Ferring Pharmaceuticals, remarked, "The ability to deliver oral peptides offers Ferring the opportunity to provide additional therapeutic choices to patients. We are impressed with Enteris's proprietary oral delivery technology and look forward to working with them to advance this development program."

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

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 has built and 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 a phase 2a-ready oral peptide, being developed for the treatment of endometriosis. For more information on Enteris BioPharma and its proprietary oral delivery technology and contract manufacturing capabilities, please visit www.enterisbiopharma.com. ■