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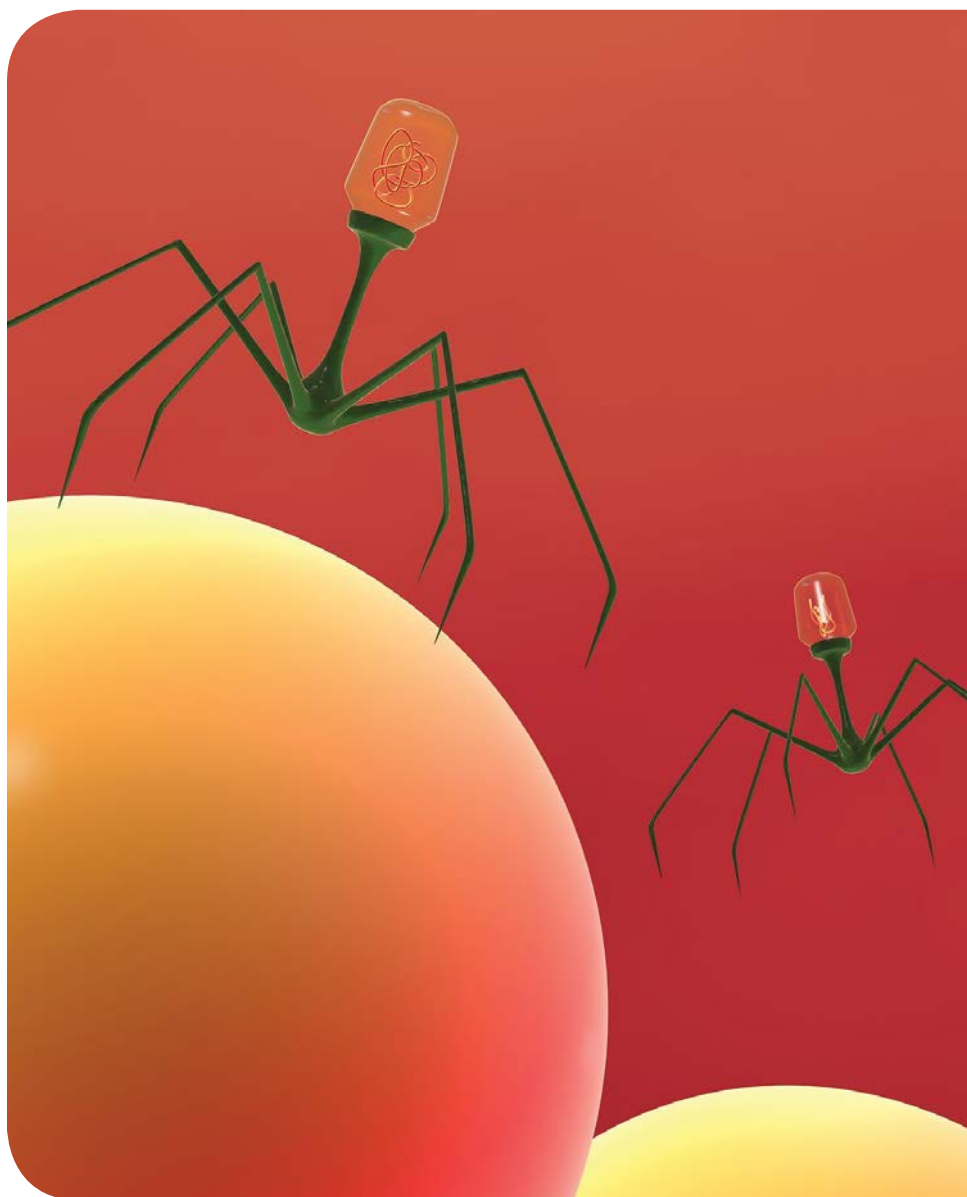
Macromolecular (Pro)drugs as Potent and Efficacious Antiviral Agents

Nanocarrier System for Oral Anticancer Drug Delivery Using Styrene Maleic Acid Micelles

Use of Dogs in the Development of Targeted Delivery Systems for Chemotherapeutics in Dogs and Man

Interview with Industry Veteran Agis Kydonieus

Feature: Delivery Method Can Reduce Drug Prices and Health System Costs



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CRS Newsletter

Leading
Delivery Science
and Technology

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Yvonne Perrie
University of Strathclyde
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Would You Put a Punt on a 5,000-to-1 Outsider?

Dear Reader,

It is one the most exciting sports stories of all time—Leicester City Football Club won the English Premier League title. For those of you outside England, you may question this statement. But the background to this is rather remarkable: Leicester started the season having just missed relegation and as 5,000-to-1 outsiders to win the Premier League title. It was a sports journey that captured the attention of many of us, even those not normally football fans. To go from “zero to hero” was a truly remarkable triumph, and you were hard pushed to find anyone who grudged them the title; how can you not love the rise of the underdogs? This sporting fairy tale has brought with it much analysis, in particular was the question “can money buy success?” Clearly not; indeed, there are several football players that played against Leicester who were each worth more than the entire Leicester team.

So what can we learn from Leicester? Well, certainly it is about working with the right people and building the team. A great scientific network can help us all develop and build our research and the impact our research can have. However, it is also about finding our supporters; we might not have the luxury of a football stadium full of passionate football fans cheering us on (and indeed that could get a little distracting), but we can work with people who motivate and challenge us to push to the next level of our research. Our support network can also help us identify and play to our strengths. It is also important we maintain and build our skills and knowledge. The good news is that all of this is what CRS is here for. Through our research community and network fostered by CRS we get the opportunity to broaden and strengthen our research networks. Indeed, within this issue of our newsletter we see reports from our local chapters and updates from a range of researchers in our field. So I hope you enjoy both this story of the underdogs and all the exciting science and news we bring you in this newsletter, and I hope you are getting ready for our meeting in Seattle.

Best regards,
Yvonne ■

An Interview with Industry Veteran and Leader of Controlled Release Technologies Agis Kydonieus

Vishwas Rai¹ and Bozena B. Michniak-Kohn²



Agis Kydonieus

Agis Kydonieus is the founder and president of Samos Pharmaceuticals LLC and cofounder of KAT Transdermals LLC and InteguRx Therapeutics LLC. He has 30+ years of extensive experience in preclinical as well as phase I–III clinical development and has launched several products in the marketplace. He has served as a consultant, scientific advisory board member, and executive for several companies in the fields of drug delivery—including oral (peptides), transdermal (passive and iontophoretic), implantable, injectable, buccal, and vaginal delivery—cancer chemotherapy, biopolymers, resorbable and nonresorbable medical devices, and tissue engineering including devices for orthopedics, adhesion prevention, ophthalmics, and wound and skin care. As a consultant, he also aids his clients in business plan preparation and venture financing, through venture groups and through strategic alliances and joint ventures.

Dr. Kydonieus secured a Ph.D. in chemical engineering in 1964 from the University of Florida and started his career as a chemical engineer at Union Carbide Corporation. In his early career, he joined Cooper Union Polytechnic Institute in New York as an assistant professor of chemical engineering, where he developed new families of polyurethane and polyester elastomers. He cofounded Chemtech, Inc., to commercialize the new polymers, which was later acquired by Morton Thiokol Inc. He joined Baxter Laboratories as an assistant director of corporate biomedical engineering before moving to HealthChem Corp., where he served as a board director, vice president, and later as president and founder for Hercon Laboratories Corporation. During his stay at Hercon Labs, company sales showed at least a 50% increase per year for over four years. During this time, he made over 50 presentations to stock exchange groups, pharmaceutical analysts, and institutional groups worldwide. His work was instrumental in obtaining a \$20 million convertible debenture for HealthChem Corp. He finally served as vice president of corporate R&D at ConvaTec, a Bristol-Myers Squibb corporation.

His work in the field of controlled release technologies has been exemplary. He is the editor of 10 books on drug delivery including the first-ever three-volume treatise on transdermal delivery and has over 70 U.S. patents and patent applications, mainly in the field of transdermal and other drug delivery technologies. His academic and industrial findings have been key foundations to various technologies in the field of formulation science, polymer science (small/large organic molecules), and medical devices. For his contributions, he has been given recognition awards by the Controlled Release Society (1990), received the BMS Outstanding Corporate Contribution Award (1992), and was elected a Fellow of CRS (2010). He has served on scientific advisory boards of multiple companies including NexMed Inc., Kytogenics Pharmaceuticals, Transport Pharmaceuticals, and Valera Pharmaceuticals and on academic boards such as the New Jersey Center for Biomaterials and the MIT Biomaterials Consortium. He is one of the founders of CRS and has served as its president (1984), program chairman of the annual meeting (1982), board member, and trustee.



CRS officers during the banquet and awards ceremony at the 1984 annual meeting.

Q During your career, which stage (company) of your career was the most exciting part of this journey and why?

A Although I have worked in large companies and in academic environments, I loved working for small companies because there was not only freedom to innovate but also the need to innovate. In a way I consider myself a serial entrepreneurial kind of person, because I always reverted back to starting a new company to accomplish what I thought was needed to advance some part of the medical field. Perhaps the most exciting company I worked for was Chemtech, because I was young and wet behind the ears, and I left a rewarding academic position to chase a dream of developing new polymers for the medical field. It was scary but rewarding at the same time, and probably it showed me the way that I followed the rest of my career.

continued

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Q Please name a few projects (of all the research projects in your career) that you have found to be both intellectually and personally satisfying.

A It seems that some of the most exciting projects came early in my career. At HealthChem we were making a three-layered polymeric laminate (with a nylon scrim in between), with the two outside vinyl layers being glued together by a vinyl plastisol. This product was accepted in many fields because of its strength and tear resistance. However, when used in moist environments it allowed fungi to grow on it, which limited its market potential. The manufacturers of the vinyl films were not interested in incorporating antifungal agents in the films because that would contaminate their manufacturing plants. So in desperation we added the antifungal agent in the plastisol glue. Amazingly enough, the antifungal agent captan migrated from the plastisol glue to the outer films and made the laminate antifungal. Washing after washing and year after year the laminate remained antifungal! Nowadays, this would be known to every student in the pharmaceutical field, but in the late 1960s this was an amazing observation. The product found its way as the covering of mattresses in hospitals and geriatric facilities and became a multimillion dollar product for HealthChem. This observation allowed for the founding of the transdermal company Hercon Laboratories, the granting of more than a dozen patents for the controlled release of active agents, and the marketing of several multimillion dollar products containing fragrances, flavors, pheromones, insecticides, and of course drugs for transdermal patches.

Q There was a short period of time when you joined academia after spending a few years in industry. What led to that transition from industry to academia and back?

A I enjoyed academia and especially teaching the young students; however, my temperament was not only to innovate and teach but also to see the innovations translated into actual products. Nowadays professors can start companies using their innovations, which I applaud and consider totally appropriate. In the early 1970s this was not something that was possible to do and in some cases not even acceptable. This is the reason that my stay as a professor was short lived, although I kept on teaching at Cooper Union for several years as an adjunct professor.

Q What are some of the current technologies you are working on that you can see as making a good impact in the market?

A Samos is working on an oral technology platform that allows the delivery of drugs for an extended period of time, such as seven days, from the administration of a single tablet or capsule. The technology is based on the development of conjugates of three molecules: the drug to be delivered, the carrier molecule, which has long half-life in the intestinal tract, and a linker with the ability to chemically bond to both the drug and the carrier molecule. The bond between the linker and the drug is designed to cleave at desired time intervals under physiologic conditions. The conjugation chemistry is being developed in conjunction with the Chemistry Department of Rutgers University, and several of the conjugates have been tested in both pigs and beagle dogs with considerable success. One U.S. patent on the technology has been granted, and others are pending. By the way, Samos is a Greek island, which my family comes from and which can arguably be considered the most beautiful island in the Aegean Sea.

I am also the president of KAT Transdermals, where we are developing seven-day transdermal patches for CNS products. Our lead products are for depression and Parkinson's diseases—with a twist, which involves drugs with different mechanisms of action. In addition, KAT has developed technologies that allow for the adhesion onto skin of any patch for a period of seven days, without concern for irritation.

InteguRx Therapeutics is also a transdermal company with proprietary technologies in the chemical enhancer area. Our first product is a transdermal gel for the prevention of nausea and vomiting in pregnancy. Patents have been granted for the product, and it has completed animal studies successfully. Unfortunately, I cannot say much more about the abovementioned products, because these are products in commercial development and trade secrets are critical for obvious reasons.

Q Where do you see the current research efforts in the pharmaceutical field being focused?

A Perhaps there are others with greater insight in this area, but my opinion is that new advances will come from point-of-care diagnostics and immunotherapy. New technologies from smart phones to lateral flow strip analyzers provide a rapid, convenient, and much less expensive way to diagnose diseases. For example, Columbia University's "dongle" can provide in conjunction with a smartphone accessory immunoassay tests for sexually transmitted diseases including HIV and syphilis. Abbott's i-STAT can conduct complete blood analysis at the point of care. Bionesa and others can provide analytic functions for infectious diseases, drug abuse, cardiac markers, blood analysis, and so on with 12 analytes being performed simultaneously, and all within 5–10 minutes. It is of course well known that the faster a disease is diagnosed the better the probability for a good outcome.

Small-molecule drugs accounted for 84% of pharmaceutical sales in 2014. However, I believe that the new research efforts and progress will now come mainly from large molecules such as antibody–drug conjugates and monoclonal antibodies that overcome suppression of the immune response and mainly for the treatment of cancer.

continued

Antibody–drug conjugates consist of a cytotoxic drug connected by a linker to a monoclonal antibody that directs it to the target cancer cells due to the great number of cell surface-associated antigens. There are a few such drugs approved by the FDA, but there are at least 40 more such conjugates presently in clinical trials.

PD-L1 is a cell surface protein that binds to the receptors PD-1 and CD80 on activated T cells and B cells and thus inhibits T cell proliferation and inhibits immune response. Overexpression of PD-L1 on cancer cells allows these cells to avoid T cell detection and elimination. Monoclonal antibodies that block PD-L1 from binding to PD-1 and CD 80 overcome the suppression of T cell activation and allow the T cells to attack the cancer. There are PD-L1 inhibitor drugs in the market already, with many more in clinical trials. I am sure that the two approaches mentioned above will keep on making ever greater impact in the treatment of cancer in the coming years.

***Q** Please tell us about your involvement with organizations such as the Controlled Release Society. Please comment on the growth of the organization over the last few decades.*

A I was involved during the prehistory and protohistory of the Controlled Release Society, being one of its founders. It all started in 1972 among seven or eight of us (N. Cardarelli, F. Wright, J. Mansdorf, J. Bakan, J. Montemarano, G. Janes, and me) who maybe accidentally found ourselves in the field of controlled release of active substances. We decided to run a symposium entitled the “International Controlled Release of Bioactive Materials Symposium.” The first symposium took place in 1974 at the University of Akron in Ohio, and it was a spectacular success. There were some 30 presentations and about 70 attendees. There was no money to operate, and the symposium was run out of the office of the Symposium Chair, with his secretary being the most important and hardest working CRS person. As a matter of fact, this continued for several years after CRS was established. We had a great number of annual meetings at the Baja Mar Hotel in Fort Lauderdale, Florida, and always in August because everything was on sale. Credit for this great innovation should be given to George Janes, who was the Arrangements Chairperson for many years. The symposium attendees reached the magic number of 100 during the fourth symposium in Corvallis, Oregon. The symposium until 1982 (320 attendees, 79 presentations) was all-inclusive, but less than 20% of the presentations and participants were in the field of drug delivery. In 1984 Joe Robinson, Bill Higuchi, Nick Peppas, and Daniel Vitaver (president of Riccar Labs, Argentina) joined the board (Linda Sanders of Syntex was also installed as CRS vice president), and CRS started to take its present trajectory.

***Q** What is your advice to the younger generations of aspiring scientists, managers, and entrepreneurs to achieve success in industry and academia?*

A This is a difficult question, because every one of us has a different understanding of what success might be. Some suggestions might be 1) don't be afraid of failure, because in the dust of failure resides the seed of success, and 2) consider that a job is nothing more than the continuation of your education. If the job becomes easy and routine, look for a promotion or a position with another company at a higher level of responsibility. To remain relevant, your career must be a continuous learning experience. Keep on learning new medical applications and technologies through course work or through job training.

***Q** Please tell us about your hobbies and your civic involvement. How have these interests helped in your personal development?*

A Other than exercising, which I do religiously to keep fit, I have two major hobbies. My wife and I are avid collectors of Chinese art. Over the last 40 years we have acquired over 500 Chinese pieces of art all the way from the Neolithic era (4000 BC) to the Shang Dynasty (2000 BC) to the Chin Dynasty (1900 AD). Recently, my son said, “Hey, Dad, your home looks like a Chinese warehouse!”

My greatest love, however, is oil painting, mainly open-air painting in Bucks County, Pennsylvania, and in the nearby New Hope and Lambertville, New Jersey, areas. I also paint still lifes in the Impressionistic style.

In the spirit of giving back to the greater society, I recently started and funded a tax-exempt foundation, “The Kydonieus Family Samos Foundation,” which provides scholarships to students of Greek descent who attend or are interested in attending the University of Florida to study chemical engineering or the sciences.



Oil painting of Hunter's Farm in Lambertville, NJ.

These hobbies allow me to relax and see the beauty of nature and the greatness of the human spirit through the ages. I get equal enjoyment executing a great painting, getting a novel technological idea, or securing a great piece of art. ■

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Macromolecular (Pro)drugs as Potent and Efficacious Antiviral Agents

Kaja Zuwala,^{a,b} Martin Tolstrup,^a and Alexander N. Zelikin^{b,c}

Macromolecular prodrugs (MP), or polymer–drug conjugates, are successful tools of drug delivery investigated broadly toward optimization of pharmacokinetics of drugs.¹ Specific advantage is gained when, for example, the polymer increases solubility of the drug or aids in localizing an enhanced payload at the desired site (e.g., tumor). Over the past years, our team developed MP for delivery of antiviral agents against hepatitis C virus (HCV), human immunodeficiency virus (HIV), and other viral pathogens (Fig. 1). Below, we outline the criteria of design and the milestones of development of these MP and identify potential avenues for further optimization of these agents.

Ribavirin (RBV) is a unique therapeutic agent with a broad spectrum of antiviral activity.^{2,3} However, this drug has an unfortunate ability to accumulate in red blood cells, causing anemia. For this reason, despite its therapeutic effectiveness, RBV has limited utility in the clinic. In our work, we aimed to optimize pharmacokinetics of RBV, specifically through conjugation with synthetic polymers. The prime rationale for this was a well-accepted notion that polymers do not enter erythrocytes. We hypothesized that conjugation to polymers (i.e., the synthesis of MP) would eliminate the origin of the main side effect of RBV. Our prime synthetic method to prepare polymers is reversible addition–fragmentation chain transfer polymerization (RAFT),⁴ such that the polymers are made uniform in size, that is, they have predictable and well-controlled properties. To make this happen, we embarked on the search for synthetic methods to prepare appropriate monomers for the synthesis (i.e., acrylates and methacrylates). The synthesis proved most efficient when employing a nature-derived catalyst, an enzyme, which afforded a 5′-derivative of RBV in high purity and yield.⁵ RBV (meth)acrylates were used to make MP based on acrylic and methacrylic acids,⁶ 2-*N*-hydroxypropyl methacrylamide,⁷ and *N*-vinyl pyrrolidone⁸ through direct copolymerization of comonomers. This approach afforded a fine control over the polymer composition and offered a high level of drug loading, up to 25 mol% of the drug-containing monomer units in the overall polymer sequence. When possible, we used high-throughput, robotic methods of polymer synthesis to screen the macromolecular parameter space and obtain MP with optimized molar mass and drug loading.^{6,7} Fluorescently labelled polymer samples were used to illustrate that MP have minor if any association with the red blood cells, thus overcoming the major side effect of RBV.^{5,7}

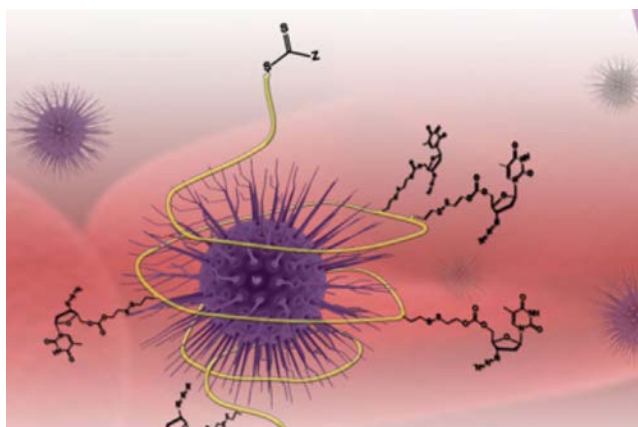


Figure 1. Artist's representation of a viral particle interacting with antiviral macromolecular prodrugs (drawn not to scale), that is, a polymer chain containing conjugated antiviral drug. Macromolecular parameter space for optimization of such prodrugs includes the chemistry of the polymer backbone and the polymer molar mass, the drug loading, and also the linkage between the drug and the carrier. Image adapted from Kock et al.¹² and reproduced by permission of The Royal Society of Chemistry.

To establish a virus-free platform to screen for activity of MP in delivering RBV, we analyzed the molecular biology and intracellular activity of this drug and identified a potential connection between RBV and the synthesis of an inflammatory marker in macrophages, namely nitric oxide.⁹ Indeed, in cell culture, RBV revealed a dose-dependent anti-inflammatory activity with EC_{50} of 7 μ M, being close to 10–20 μ M plasma level quoted as physiologically relevant for patients on RBV treatment. These experiments also highlighted that RBV has a dramatically narrow therapeutic window; toxicity related IC_{50} was only marginally higher than EC_{50} and was established at 14 μ M. Using this assay, we revealed that MP tremendously broadened the therapeutic window of RBV. However, it also became obvious that potency of (meth)acrylate-based MP was well below that of the pristine drug, highlighting a need to engineer faster and more quantitative drug release.

We addressed this challenge using a cunning tool of organic chemistry, namely, self-immolative linker (SIL) technology.¹⁰ Further to the most celebrated attribute of SIL, accelerated kinetics of drug release, this tool allows to temporarily and reversibly install “un-natural” chemistry into drug molecules, such as disulfide chemistry into thiol-free drugs. Indeed, RBV and the overall majority of drugs on the market are devoid of thiol

continued

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functionality. Yet with the use of the SIL, we were able to engineer disulfide reshuffling—a specific intracellular trigger for drug release—into successful antiviral MP for delivery of RBV¹¹ as well as azidothymidine¹² (against replication of HIV) and panobinostat¹³ (an HIV latency reversing agent). For RBV, this designed MP exhibited potent activity in both inhibiting inflammation in macrophages and inhibiting replication of the HCV RNA in hepatocytes, toward a concurrent treatment of hepatitis and against HCV.¹¹

Subsequent development of MP of RBV based on poly(methacrylic acid) led us realize that these agents may have a broad spectrum of antiviral activity, a highly sought after therapeutic characteristic (Fig. 2).¹⁴ Indeed, polyanions have a decades-long history of use as microbicides, achieved through nonspecific extracellular association with the viral particles.¹⁵ In turn, RBV is one of the few agents with documented activity against several viral pathogens,³ making the designed polyanionic MP truly unique in that both the polymer and the conjugated drug potentially exhibit antiviral effect. Furthermore, our studies revealed that these MP act as inhibitors of polymerases, owing to the anionic charge of the polymer, making up MP with triple activity against viruses.¹⁶ We put the MP to a test and successfully illustrated their ability to prevent infectivity of influenza, measles, respiratory syncytial virus, hepatitis C (replicon), and Ebola. Lead candidate MP were tested in chicken embryo to reveal successful inhibition of the influenza virus in this pre-*in vivo* model.¹⁶ In collaboration with several virology partners, we are now investigating the scope of these MP as broad spectrum antiviral agents.

Taken together, our efforts to date established the tools to design potent, efficacious prodrugs for delivery of diverse antiviral agents. We are now investigating the potential of these agents against diverse viral pathogens and associated diseases in animal models, and we would welcome further opportunities in collaborative projects within diverse areas of biomedicine.

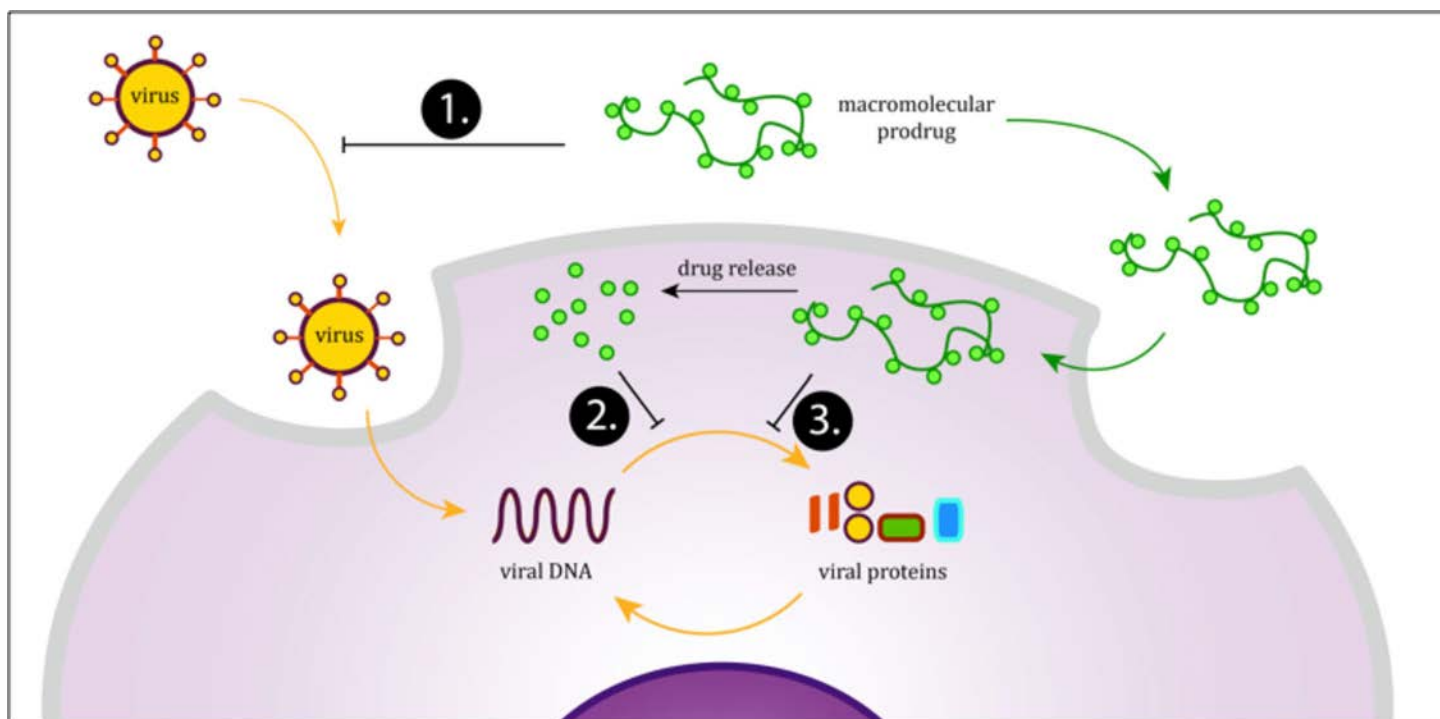


Figure 2. Polyanionic macromolecular prodrugs developed in this work exhibit three modes of activity against viral pathogens: 1, extracellular inhibition of virus cell entry through interaction of the polymer with the viral particles; 2, intracellular activity through the release of the conjugated drug (e.g., inhibition of reverse transcriptase by the released azidothymidine); and 3, intracellular activity through competitive inhibition of polymerases by the polymer chain owing to high anionic charge of the polymer.

Acknowledgements

We acknowledge financial support from the Danish Council for Independent Research, Technology and Production Sciences, Denmark (ANZ; project DFF – 4184-00177).

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Nanocarrier System for Oral Anticancer Drug Delivery Using Styrene Maleic Acid Micelles

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Introduction

Oral administration of anticancer drugs is preferred by patients due to its noninvasive nature. Oral drug delivery can also be tailored to maintain plasma concentrations above therapeutic level and ensure prolonged and effective exposure of cancer cells to the chemotherapeutic agent. However, significant limiting factors are associated with the oral administration of anticancer drugs such as their low bioavailability¹ and local toxicity to the gastrointestinal (GI) tract.² The encapsulation of these anticancer drugs into a nanomicelle carrier should decrease the toxicity to the GI tract. Also, nanosized formulations take advantage of the wide fenestrations of tumor vasculature and the impaired lymphatic drainage to selectively accumulate in the tumor tissue, in turn improving the therapeutic efficacy and safety of these drugs. Despite a plethora of research being dedicated to the development of nanosized formulations, there is still no oral anticancer nanomedicine in clinical use.

Experimental Methods

Synthesis and Characterization. Poly(styrene-*co*-maleic acid) (SMA) micelles were synthesized in a pH-dependent process.³ Loading of epirubicin (Epi) or the fluorescent dye dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate (DiI) was determined by a spectrofluorometer at 480 and 544 nm, respectively. Size and zeta potential were determined with a Malvern Zetasizer. Release rate was determined by solubilizing the SMA-Epi (1 mg/mL) in water or simulated gastric fluid (0.2% [w/v] NaCl in 0.7% [v/v] HCl, deionized H₂O, pH adjusted to 1.6).

In Vitro Model of the Intestinal Epithelium. Caco-2 cells were seeded onto Transwell plates and maintained for 21 days to achieve a differentiated cell monolayer. SMA-Epi (100 μ M) was added to the apical compartment for 3 h. The transport was quantified by measuring the content of Epi released in the basolateral compartment. Transport mechanisms were also evaluated with inhibitors of endocytosis mediated through clathrin (dansylcadaverine) and caveolin (genistein) or micropinocytosis inhibitors (amiloride) (100 μ M).

Ex Vivo Model of the Intestinal Epithelium. Sections of the rat intestine were everted. Sacs filled with 1 mL of Hanks balanced salt solution (HBSS) were immersed in 10 mL of the SMA-Epi solution (100 μ M) in HBSS supplied with carbogen. The transport of SMA micelles was measured after 3 h.

In Vivo Mechanism of Transport of SMA Micelles. Balb/c female mice (6 weeks) were randomly divided into two groups receiving either free DiI or SMA-DiI by oral gavage (15 mg/kg). Animals were euthanized after 8 h. For immunohistochemistry, tissue sections were incubated with *Ulex europaeus* lectin antibody conjugated with biotin (UEA1), followed by treatment with streptavidin and development by 3,3'-diaminobenzidine (DAB). The isolated Peyer's patches were imaged for the DiI fluorescence and then stained with hematoxylin and eosin (H&E) stain.

Statistics. Groups were compared using unpaired *t* test or one-way ANOVA coupled with the Bonferroni post-hoc test, using GraphPad Prism 6 software (*P* < 0.05).

Results and Discussion

The SMA micelles synthesized had loadings of 7.5 and 18% of Epi and 12.11% of DiI as determined by weight/weight ratio. The mean diameters were 21.5 ± 4.2 and 80.8 ± 10.1 nm for 7.5 and 18% loadings, respectively, and 134.1 ± 2 nm for SMA-DiI. The size of these SMA micelles was suitable to escape renal clearance and prolong their presence in the circulation. All micelles had a neutral charge to decrease opsonization. The 7.5% loaded SMA-Epi micelle had a higher transport across the differentiated Caco-2 cell monolayer compared with the 18% loaded SMA-Epi micelle (Fig. 1).

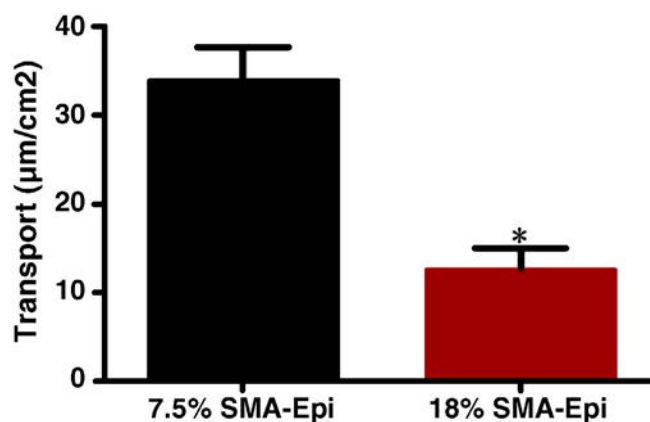


Figure 1. The transport of 7.5% and 18% SMA-Epi after 3 h of treatment across an in vitro model of intestinal epithelium. Asterisk (*) indicates significance at *P* < 0.05.

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Pretreatment with inhibitors of clathrin-dependent endocytosis or micropinocytosis resulted in a reduction in transport of 18% loaded SMA-Epi micelles by 54 and 32%, respectively (Fig. 2A). Moreover, isolated rat jejunum sections had 10.1 and 2.7% transport of 7.5 and 18% loaded SMA-Epi, respectively. Also, the ileum sections showed 11.9 and 4% transport of 7.5 and 18% loaded SMA-Epi, respectively (Fig. 2B).

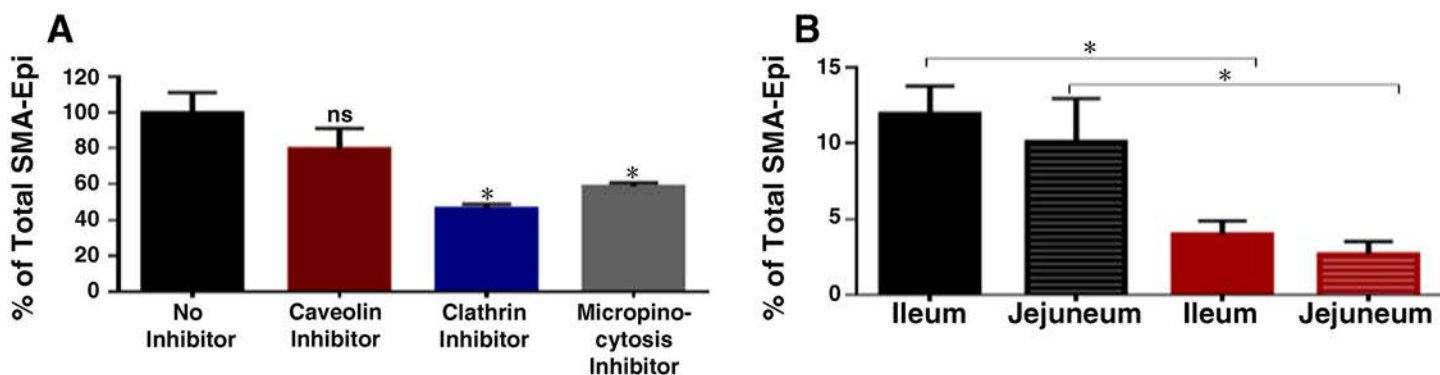


Figure 2. (A) Transport of SMA micelles across differentiated Caco-2 monolayer after 1 h pretreatment with endocytosis inhibitors followed by 3 h incubation with 18% SMA-Epi. (B) Transport of 7.5 and 18% SMA-Epi through ileum and jejunum sections of rat intestine (*ex vivo*) after 3 h of treatment. Asterisk (*) indicates significance at $P < 0.05$; ns = not significant.

The immunohistochemistry of intestinal sections showed that the fluorescence of SMA-DiI overlapped with M-cells identified with UEA-1 antibody, indicating the uptake of SMA-DiI involved M-cells lining the intestinal villi. In addition, accumulation of SMA-DiI was observed underneath the epithelium lining of Peyer's patches (Fig. 3).

Conclusions

Our data showed that SMA micelles are transported across an *in vitro* model of the intestinal epithelium mediated by clathrin-dependent endocytosis and micropinocytosis. In addition, colocalization of SMA-DiI with M-cells and its accumulation in Peyer's patches were observed. Overall, these data confirm the capability and

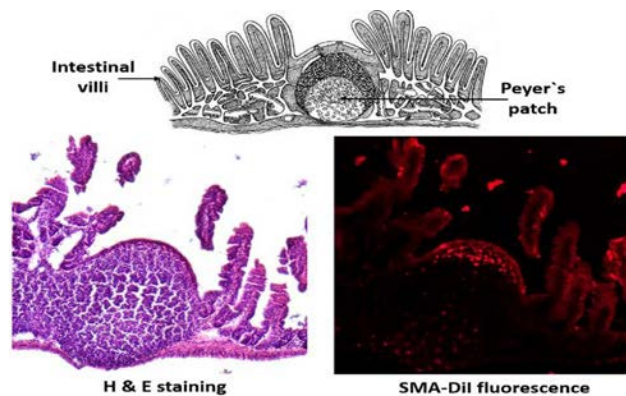


Figure 3. SMA-DiI fluorescence was seen in the Peyer's patches isolated from intestinal sections of mice treated with SMA-DiI (15 mg/kg) by oral gavage.

Acknowledgements

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Use of Dogs in the Development of Targeted Delivery Systems for Chemotherapeutics in Dogs and Man

Marilyn Martinez^a and Terry Bowersock^b

The first report of cancer chemotherapy for dogs was published in 1946 (the use of urethane to treat hematopoietic neoplasia in a dog).¹ Today, there are numerous examples where studying potential cancer therapies or therapeutic targets for the treatment of canine carcinomas has supported corresponding therapies in human patients, including the following:²

- Signal transducer and activator of transcription 3 (STAT3) is a transcription factor that mediates signal transduction to the nucleus in response to cytokine and growth factor receptor binding. STAT3 regulates genes involved in cell proliferation, apoptosis, angiogenesis, and immune responses, and it is found in multiple osteosarcoma (OSA) tumor cell lines of dogs and people.³ Down regulation of phosphorylated STAT3 induces cell-growth arrest and apoptosis in canine and human OSA cell lines, supporting its potential as a target for therapeutic intervention in dogs and humans.
- Toceranib phosphate is an orally bioavailable small molecule inhibitor that blocks several receptor tyrosine kinases. In addition to confirmation of effectiveness, work with toceranib in dogs established the pharmacokinetic/pharmacodynamic (PK/PD) endpoints that supported subsequent work on sunitinib inhibitors in people.
- Selinexor (KPT-330) and verdinexor (KPT-335) are orally bioavailable selective inhibitors of nuclear export that reversibly block exportin-1 function. Initial studies in dogs with lymphoma demonstrated clinical benefits with dose-limiting toxicities related to manageable anorexia and weight loss. The data from these canine studies were included in the Investigational New Drug (IND) application for selinexor. The clinical toxicities and responses seen in dogs were highly predictive of those observed in people treated with selinexor.
- A xenogeneic tyrosinase DNA vaccine was developed for the treatment of canine malignant melanoma. The xenogeneic human tyrosinase DNA vaccine (ONCEPT™ canine melanoma vaccine, Merial) received USDA approval in 2007, becoming the first and only USDA-approved therapeutic vaccine for the treatment of cancer in either dogs or humans. It supported subsequent human clinical trials using a xenogeneic tyrosinase DNA vaccine for human malignant melanoma.

Our first two articles explored the relationship between canine and human health. In the first article,⁴ we described the similarities of diseases seen in dogs and people, while the second article⁵ discussed the naturally occurring canine cancers as models of homologous human cancers. In this third and final article, we consider the importance of parallel canine–human therapeutic product development to help identify novel delivery systems and chemotherapeutic targets for the treatment of canine and human cancers.

Examples of Novel Delivery Systems and Therapeutic Options Studied in Dogs

Liposome Encapsulated Muramyl Tripeptide.^{6,7} This lipophilic derivative of muramyl dipeptide is a synthetic analog of a mycobacterium cell wall component that is incorporated into liposomes. It functions as an *immune stimulator*. Both in a double-blind placebo-controlled clinical trial of liposomal encapsulated muramyl tripeptide-phosphatidyl ethanolamine (L-MTP-PE) in 27 dogs and in a trial in dogs that underwent amputation and received this treatment in conjunction with cisplatin, a statistically significant improvement in overall survival time was observed. The results of these studies formed the basis for phase 2 and phase 3 clinical trials of L-MTP-PE in children with OSA.²

“STEALTH” Liposomes.⁸ These PEGylated liposomes are formulated to *avoid uptake by monoclonal phagocytes*, thereby increasing circulation time. Given their size, these liposomes selectively enter the tumor via the higher vascular permeability in cancer tissues, reducing systemic toxicity. Although STEALTH liposome-encapsulated cisplatin enabled a fivefold increase in the maximally

continued

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

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

tolerated dose in OSA dogs, there was no difference in terms of clinical outcomes. Nevertheless, this study succeeded in demonstrating the therapeutic potential of this system.

Overcoming Drug Resistance.⁹ One of the most important causes of ineffective chemotherapy treatment of OSA is multidrug resistance (MDR). As a result, silencing MDR1 mRNA expression is an approach for *overcoming MDR*. By employing nanoparticles with a size <100 nm, a therapeutic agent can be introduced into the cell, bypassing the efflux pump and entering the neoplastic cells through endocytosis. For example, using a human OSA cell line, Susa *et al.*¹⁰ showed that both doxorubicin and siRNA encapsulated in liposome-based dextran nanoparticles cause the simultaneous suppression of drug efflux pumps and have higher cytotoxic effect on both drug-sensitive and drug-resistant OSA cells. Similar nanotechnology has been developed for use in dogs.

Use of Imaging to Explore the Permeability and Retention of Antitumor Medications.¹¹ The success of efforts to develop nanocarriers that can deliver drugs to cellular and subcellular targets in solid tumors necessitates methods for *confirming drug enhanced permeability and retention* (EPR). Currently, there is little appreciation of the differences in EPR effects as a function of tumor types, the heterogeneities within each patient group, and the dependency on tumor development stage in humans. However, much of this necessary understanding can be promoted by studying dogs with spontaneously occurring solid tumors. A novel loading method of copper-64 into PEGylated liposomes was used to evaluate the EPR effect in 11 canine cancer patients with spontaneous solid tumors using PET/CT imaging. This study provided the first high-resolution analysis of EPR-based tumor accumulation in large animals. The results confirmed that although the EPR effect is strong in some tumor types, there is a high degree of heterogeneity between tumors. Six of seven carcinomas displayed high liposomal uptake, whereas only one of four sarcomas displayed signs of liposome retention. Thus, it was concluded that nanocarrier radiotracers could serve as a tool for identifying those cancer patients that would potentially benefit from nanocarrier-based therapeutics in clinical practice.

Convection-Enhanced Delivery (CED).¹² Since canine spontaneous glioma bears marked similarities to the human tumor counterpart, CED of liposomal nanoparticles containing a topoisomerase inhibitor was evaluated to ascertain its ability to *treat cancers of the brain*. To facilitate visualization of intratumoral infusion, magnetic resonance imaging (MRI) was employed. The assessment of liposomal delivery was evaluated by the use of liposomes loaded with the contrast agent gadoteridol. It was determined that the critical factor limiting distribution within tumor tissue was the leakage of infusate into low-pressure systems such as the ventricular or subarachnoid spaces. Decreased tumor volume, tumor necrosis, and modulation of tumor phenotype correlated with volume of distribution of infusate (Vd), infusion location, and leakage (as determined by real-time MRI and histopathology). Variability in Vd between tumors strongly suggested that real-time imaging is an essential component of CED therapeutic trials to minimize the inappropriate administration of infusions and to support accurate assessments of clinical outcomes.

Tumor Immunotherapy.^{13,14} The programmed cell death ligand (PD-L1) is a transmembrane protein that suppresses immune response by binding to the corresponding receptor on PD-1 on T cells, B cells, and myeloid cells, thereby modulating or inhibiting their activity. The binding of PD-L1 to PD-1 prevents the activation of T cells, reducing autoimmunity and promoting self-tolerance. Therefore, the expectation is that inhibiting the activity of this receptor will *promote the immune-mediated phagocytosis and death* of tumor cells. Fourteen canine tumor cell lines, as well as primary cultures of canine monocytes and macrophages, were evaluated for constitutive PD-L1 expression and for responsiveness to immune stimuli. Although PD-L1 was constitutively expressed on all evaluated canine tumor cell lines (i.e., its corresponding gene was continuously transcribed), the levels of basal expression (the formation of a functional gene product) were variable. Significant upregulation of PD-L1 expression by all tumor cell lines was observed following interferon- γ (IFN- γ) exposure and by exposure to a toll-like receptor ligand. Canine monocytes and monocyte-derived macrophages did not express PD-L1 constitutively but did significantly upregulate expression following treatment with IFN- γ . These findings are consistent with current beliefs that the upregulation of PD-L1 expression can be a mechanism mediating T cell suppression and that potential mechanisms for either inhibiting or bypassing this effect may be via the use of monoclonal antibodies or by autologous infusion of manipulated T cells. Several potential strategies for manipulating the immune system response exist.

Anticancer Vaccines.

- **DNA Vaccines.**¹⁵ Compared with other types of vaccines, those involving DNA can induce both humoral and cellular immunity. To this end, a vaccine was developed to *stimulate macroautophagy* (a process in which cellular contents are degraded by lysosomes or vacuoles and recycled)¹⁶ and to influence several signal transduction pathways. In particular, tumor cells are highly dependent on the protein p62, but normal cells are not dependent upon this protein. Since down regulation of the protein p62 causes inhibition of growth or loss of viability of the tumor cells, an anticancer DNA vaccine based on p62 was developed. Tested in seven unspayed female dogs with mammary tumors, the vaccine was found to be safe and effective.
- **Recombinant Listeria Vaccine.**¹⁷ The dog can also serve as an important model for forwarding therapeutic options for the treatment of pediatric OSA. Human-canine commonalities in OSA include tumor genetic instability and histologic heterogeneity of the tumor,

aggressive local disease, early metastases, and micrometastases. *HER2/neu* is a tyrosine kinase receptor that belongs to the family of epidermal growth factor receptors which is frequently overexpressed in carcinomas of the breast, prostate, pancreas, and gastrointestinal tract. Its overexpression is linked to a human–canine reduced response to neoadjuvant chemotherapy, high metastatic rates, and shorter overall survival times. *Listeria monocytogenes* (*Lm*) is a facultative anaerobic, intracellular bacterium that infects mononuclear cells and is a potent stimulator of innate and adaptive immunity. Once in the phagosome, *Lm* secretes the pore-forming lysis listeriolysin O, which enables the vaccine to escape into the cytosol. It can lead to the priming of CD8+ and CD4+ T cells, respectively. Intravenous administration of up to 3.3×10^9 CFU of ADXS31-164 was well tolerated, broke peripheral tolerance to *HER2/neu*, and was highly effective at preventing pulmonary metastatic disease when administered to 18 dogs with *HER2/neu*+ appendicular OSA. Observed toxicities were low grade and transient. Overall survival was significantly prolonged in treated dogs when compared with a matched historical control group and previously published reports. These findings represent a major advance in the search for *preventative therapies for metastatic OSA* in dogs and children.

Canine Parvovirus as a Drug Delivery Device.¹⁸ Viral particles are being considered for the purpose of serving as multifunctional nanodevices that will *specifically recognize tumors and thus enable early diagnosis and provide targeted treatment* of this disease. The goal is to reduce problems of toxicity and inadequate effectiveness through tumor targeting. Many therapies depend upon the potential for leaky vasculature to obtain a more targeted drug delivery. However, receptor-mediated endocytosis may serve as a more specific and efficient process. A challenge associated with the use of targeted tumor delivery is that it is dependent upon the binding of a ligand to a cell-specific receptor in order to initiate the process of internalization. In this regard transferrin (Tf) is a circulatory iron-carrier protein that is in great demand for rapidly proliferating cells, such as cancer cells. As demand increases, there is an upregulation of the Tf receptor. Springboarding from this point, it is recognized that virus-based systems can be modified so as to achieve tumor-specific interactions. Interestingly, canine parvovirus has a natural affinity for transferrin receptors (TfRs) (both of canine and human origin), and this property could be harnessed because TfRs are overexpressed by a variety of human tumor cells. Thus, the canine parvovirus may be a mechanism for future drug delivery.

Concluding Thoughts

Unlike rodent models, the dog represents a naturally occurring model of human cancers. Not only are the cancers histologically and genetically similar but they also typically exhibit similar response to anticancer therapies. In addition to the development of new therapeutic strategies, the use of canine clinical oncology trials provides a number of other valuable benefits, including:¹⁹

- Evaluating the use of biomarkers in clinical trials and the utility of biomarkers as surrogates for establishing drug PD and/or PK/PD relationships.
- Exploring the challenges and opportunities for imaging to support clinical trials.
- Identifying variables that can influence the outcome of clinical trials.

The dog has been and continues to be invaluable in the search for cancer treatment for humans, and likewise, the human has been invaluable for the search for potential cancer treatments in dogs. Understanding these relationships and how to maximize the information to support efficient product development is essential. It is with these points in mind that our 2016 workshop session titled “Developing Therapeutic Options for Combating Cancer: A ‘One Health’ Challenge for Humans and Dogs” provides an opportunity to explore potential treatments of canine cancers, what canine research has taught us about the disease progression and potential treatments, and how the development of therapeutics for cancer in dogs serves as an invaluable platform for new avenues of treatment for humans.

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CRS Election Results

The 2016 CRS election votes have been tallied and the results finalized. The nomination process, led by the Nominating Committee headed by Arthur J. Tipton, allowed for many opportunities for member input. The newly elected Board of Directors, listed below, will begin their new positions on July 20, 2016, at the conclusion of the annual meeting. Thank you to all the impressive candidates who participated in this election. Thank you to all the members who voted this year, helping to shape the future of our society.

Congratulations to our newly elected CRS Board



President-Elect
Tamara Minko
*Rutgers University,
U.S.A.*



Treasurer-Elect
Julius F. Remenar
*Alkermes, Inc.,
U.S.A.*



Secretary
Maria Jose Alonso
*University Santiago de
Compostela, Spain*



Director-at-Large
Richard Korsmeyer
Pfizer, Inc., U.S.A.



Director-at-Large
Mark Prausnitz
*Georgia Institute of
Technology, U.S.A*

In addition to the newly elected Board members listed above, the following CRS members are also serving on the 2016–2017 Board.

President
Ruth B. Schmid
SINTEF, Norway

Director-at-Large
Justin S. Hanes
Johns Hopkins University, U.S.A.

Immediate Past President
Debra J. Bingham
Valeo Partners, U.S.A.

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Director-at-Large
James D. Oxley
Southwest Research Institute, U.S.A.

Delivery Science Can Play a Significant Role in Patient-Focused Innovation While Reducing Drug Prices, Health System Costs

Michael D. Hooven, CEO, Enable Injections, U.S.A.

Cost savings and reputation are top of mind at every pharmaceutical company, particularly in light of the highly charged topic of drug prices. In this, an election year, the biopharmaceutical industry is coming under increased scrutiny from left, right, and center. Companies such as Valeant and Turing Pharmaceuticals have been fiercely criticized for acquiring drugs, then dramatically raising prices simply to maximize profits—at the expense of patients. It's no wonder that at political rallies, attacks on pharmaceutical companies draw cheers and thunderous applause.

Better to earn thunderous applause for patient-focused innovation.

What does this have to do with delivery science? A great deal. With more rapid adoption of new drug delivery technology, delivery scientists can significantly reduce drug development and healthcare costs, shorten formulation time, and—most importantly—promote compliance by adding patient-pleasing delivery options.

A Price Waterhouse Cooper (PWC) survey of 76 pharmaceutical executives in 13 countries exhorts the industry to innovate beyond finding new drug candidates—by creative partnering, for example.

“The returns on effective innovation are huge,” the study authors wrote. “We found a clear correlation between innovation and growth ... the top 20% of innovators in our overall survey anticipate three times as much growth as the bottom 20% over the next five years. A clear majority of our (C-suite) pharma respondents (86%) say innovation is important to their business.”

I would argue that the world of drug delivery is ripe for disruption.

Change the Topic from Gouging to Helping Alleviate Concerns

While the case of former Turing CEO Martin Shkreli raising prices on Daraprim, a drug to treat cancer and AIDS, by 5,000% may be an extreme example, the high cost of drugs is a constant worry for many patients. In a 2015 Kaiser Permanente poll, drug prices—particularly for chronic diseases—were among patients' top concerns. And governments are listening. In Massachusetts, newly proposed legislation, the first of its kind in the nation, would force biopharma companies to justify their prices by disclosing how much they spend on research, manufacturing, and marketing.

Pharma's standard defense—the hurdles and high costs of developing new and better therapies—falls largely on deaf ears. Consumers wonder whether these advances will be affordable. Payers worry that large-scale payouts for expensive medications could bankrupt them.

Yet these drug price fears coincide with rapid progress by the biopharmaceutical industry in developing promising and desirable products that could improve survival and quality of life. Currently more than 900 biologics are in development to better treat cancers, autoimmune diseases, and rare and chronic diseases. Analysts forecast that by the end of this year, 50% of the top 100 drugs will be biologics.

Combining these drugs with compelling drug delivery innovation can change the conversation from gouging to patient-centricity, cost savings, and value.

Delivery Technology Can Help Lower Drug Development Costs

An entirely new class of drug delivery technology has recently been introduced and is now available for R&D and clinical studies: wearable high-volume drug delivery devices. This technology offers a simple, comfortable, at-home treatment option for patients. For formulation teams developing injectable biologics and high-volume drugs up to



The Enable Injector fills automatically.

50 mL, the new drug delivery technology makes development of stable, bioavailable, clinically relevant formulations easier, faster, and less costly.

It brings to market a novel way to cut costs while adding overall value to the healthcare system, resolving drug formulation challenges by:

- Delivering more volume *subcutaneously*
- Delivering more viscous, high-concentration proteins *subcutaneously*
- Providing long-term stability at room temperature
- Offering product differentiation in a competitive market
- Providing customizable drug delivery rate and duration for absolutely minimal patient discomfort
- Enabling a simpler method of product preparation

Additionally, wearable high-volume injectors, also known as on-body delivery systems, accelerate or eliminate tedious, time-consuming formulation functions for more rapid—and less costly—product development.

Partnering with a Drug Delivery Company to Raise Patient Satisfaction

The new delivery option offers a differentiated product and, potentially, product extensions that please patients. An infusion that today would require a time-consuming trip to a healthcare facility and a 30–60 minute IV treatment could be completed at home in minutes at much lower cost and far greater convenience, with never a needle in sight.

The three-step delivery process is simple for a patient or nonmedical helper to accomplish. The steps are:

1. Insert any standard vial, cartridge, or syringe into a container that automatically warms any refrigerated drug in the 30–40 seconds it takes to fill the on-body delivery system.
2. Once the on-body delivery system is filled, adhere the injector to the skin under clothing.
3. Push one button to begin the delivery. Mobility is unrestricted during delivery.

CSL Behring Partners for Innovative Drug Delivery

Global specialty drug maker CSL Behring sought to differentiate a large-volume product in their pipeline and place the company squarely at the forefront of patient-focused biopharmaceutical companies. Patient panels sampled drug delivery options, choosing injection comfort and convenience as key preferences. The company subsequently struck a development deal with Enable Injections, who after performing more than 60 human factors studies, engineered patient comfort into a small, wearable, high-volume on-body delivery system. Enable's novel technology was also proven compatible with CSL Behring's product.

Delivery Technology Can Help Raise Profitability by Boosting Compliance

Human factors engineering of products plays a prominent role in increasing and ensuring patient satisfaction. Just as Amazon changed consumer buying habits, so patient-friendly wearable high-volume injectors can change patients' acceptance of injection regimens. Because of their ease of use and comfort, the new injectors are widely expected to boost compliance, which may lead to improved outcomes, the ultimate goal of any treatment.

The route to blockbuster biologics lies in addressing patient needs through human factors engineering of easy-to-use, convenient, and comfortable delivery systems.

There is a growing consensus that the pharmaceutical industry's traditional cost-cutting and productivity enhancement methods have run their course. Facing the challenge of finding the right balance between volume and viscosity while maintaining quality and stability, development teams can save millions of dollars by adopting new drug delivery technology that not only enhances patient satisfaction, compliance, and convenience but also removes much of the added cost and effort of developing large-volume drugs.

The PWC study found that society, investors, and patients have an insatiable appetite for pharmaceutical innovation. Delivery scientists and engineers adopting promising new patient-focused technology can help light the way. ■



Patients adhere the auto-filled injector to their body and push one button. The device delivers large-volume biologics easily and comfortably at home, at work, or on the go.



THE DIFFERENCE BETWEEN A SOLUTION AND THE RIGHT SOLUTION.

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Companies in the News

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

May

BioDelivery Sciences and Collegium Pharmaceutical Announce the Signing of a Licensing Agreement for ONSOLIS® in the United States

PRNewswire: May 11, 2016 – RALEIGH, NC, U.S.A. – BioDelivery Sciences International, Inc. (Nasdaq: BDSI) and Collegium Pharmaceutical, Inc. (Nasdaq: COLL) today announced the signing of a licensing agreement under which BDSI is granting the exclusive rights to develop and commercialize ONSOLIS® (fentanyl buccal soluble film) in the United States to Collegium.

ONSOLIS is an opioid agonist indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Under terms of the agreement, Collegium will be responsible for the manufacturing, distribution, marketing, and sales of ONSOLIS in the United States. Both companies will collaborate on the ongoing transfer of manufacturing, which includes submission of a Prior Approval Supplement (Supplement) to the U.S. Food and Drug Administration (FDA). Upon approval of the Supplement, the New Drug Application (NDA) and manufacturing responsibility will be transferred to Collegium.

Financial terms of the agreement include:

- \$2.5 million upfront nonrefundable payment, payable to BDSI within 30 days;
- Reimbursement for a predetermined amount of the remaining expenses associated with the ongoing transfer of manufacturing of ONSOLIS;
- \$4 million upon first commercial sale of ONSOLIS in the United States;
- Up to \$17 million in potential payments based on achievement of performance and sales milestones;
- Upper-teen percent royalties based on various annual U.S. net sales thresholds.

“We are very pleased to enter into this important partnership with a company that has a focus in the pain management area, through their recent FDA approval of Xtampza™ ER, an approved abuse-deterrent opioid, and their commitment to the pain category,” said Dr. Mark A. Sirgo, president and chief executive officer of BDSI. “We believe there remains a significant need for novel delivery technologies for the treatment of breakthrough cancer pain, and we look forward to ONSOLIS potentially returning to the market by mid-2017.”

“ONSOLIS is highly complementary to Xtampza™ ER as it allows us to leverage our commercial infrastructure. Many physicians treating patients with cancer-related persistent pain using extended-release oral opioids also need to manage breakthrough pain and can do this effectively with transmucosal immediate-release fentanyl. Adding this product to our portfolio contributes to our mission of supporting responsible opioid prescribing for patients requiring opioid pain therapies,” said Michael Heffernan, chief executive officer of Collegium. “The timing of the potential ONSOLIS launch, expected in mid-2017, allows us to focus the commercial organization on the launch of Xtampza ER for at least the next 12 months.”

Elixir Medical Corporation to Showcase the Next-Generation Bioresorbable Novolimus-Eluting Coronary Scaffold Systems

Business Wire: May 11, 2016 – SUNNYVALE, CA, U.S.A. – Elixir Medical Corporation, a developer of products that combine state-of-the-art medical devices with advanced pharmaceuticals, announced today that it will showcase demonstration of the next-generation 120 µm thin-strut bioresorbable scaffold system, DESolve CX, at EuroPCR in Paris. EuroPCR is the annual meeting of the European Association for Percutaneous Cardiovascular Interventions.

The Elixir TNT Symposium scheduled for Tuesday, May 17, at Theatre Bleu, will also feature the world's first fully bioresorbable scaffold system specifically designed for AMI (acute myocardial infarction) patients, the AMITY® novolimus-eluting coronary scaffold system, in addition to follow-up results from the DESolve® NX study at 3 years, and pipeline clinical programs.

continued

Elixir Medical Corporation, a privately held company headquartered in Sunnyvale, California, develops products that combine state-of-the-art medical devices with advanced pharmaceuticals to provide innovative treatment solutions to patients worldwide. The company's next-generation drug-eluting stent systems and bioresorbable coronary scaffold are designed to optimize localized drug delivery to provide safe and effective treatments for cardiovascular patients. For more information, visit www.elixirmedical.com.

Nitto Signs Partnership Agreement with Daiichi Sankyo

Business Wire: May 10, 2016 – OSAKA, Japan – Japan's leading diversified materials manufacturer Nitto Denko Corporation (TOKYO: 6988)(ISIN: JP3684000007) today announced the signing of a partnership agreement with global pharmaceutical company Daiichi Sankyo Company, Ltd. (hereafter "Daiichi Sankyo") that will utilize Nitto's proprietary PassPort® active transdermal drug delivery technology.

Based on this agreement, Nitto will provide exclusive rights to the PassPort® system for an undisclosed compound owned by Daiichi Sankyo and will support clinical development of the candidate in the United States. Nitto will be responsible for manufacturing the innovative transdermal patches and device components associated with the product. Financial terms were not disclosed.

The PassPort® system is designed to provide transdermal delivery of therapeutics that are typically limited to invasive and often painful injection or infusion methods. In addition to being convenient for both patients and caregivers, Nitto's technology aims to provide a new option for compounds with administration issues.

Going forward, Nitto will continue to accelerate the commercialization of its novel drug delivery system through the partnership agreement with Daiichi Sankyo.

The PassPort® system is a patented drug delivery platform that combines thermal microporation technology—to painlessly create micropores on the surface of the skin—with advanced drug patch technology. Unlike existing passive transdermal patches, the PassPort® system enables efficient delivery of a wide range of pharmaceuticals including small molecules, peptides, proteins, carbohydrates, and oligonucleotides. The result is a novel technology for needle-free administration of drugs that are currently only available via injection or infusion.

The minimally invasive PassPort® system is able to control drug delivery by optimizing several parameters including the number of micropores, patch size, and formulation. The system may be designed to produce either immediate or sustained delivery profiles that can mimic conventional injection products. Using a small handheld PassPort® device, patients are able to conveniently self-administer medication since it is easy to apply and the micropores are safely created within a few milliseconds.

Using features of the PassPort® system designed to maintain a steady drug concentration in the bloodstream and improve ease of use, Nitto plans to create new products for challenging compounds that are difficult to deliver using traditional routes of administration. In collaboration with pharmaceutical and biotechnology companies, Nitto will continue to contribute to customers' value creation with innovative ideas in the life sciences area.

Founded in 1918, Nitto Denko Corporation is Japan's leading diversified materials manufacturer and offers high-value-added products to various industries in the global market. Fully utilizing core technologies such as adhesion and coating, Nitto develops and manufactures transdermal patch products that allow pharmaceuticals to be absorbed through the skin and delivered systemically or to local target sites. Nitto's products for the treatment of asthma and angina hold top prescription market share for commercial patches.

Transdermal patches have many advantages over alternative routes of administration and have been shown to improve patient adherence to medication, as well as reduce systemic side effects by maintaining a steady drug concentration in the bloodstream. Recognizing these benefits, Nitto established an active transdermal technology platform (PassPort® system) to further expand potential drug candidates for transdermal patch delivery and continue to create novel pharmaceutical products. For additional information regarding the PassPort® technology, please visit www.nitto.com/jp/en/press/2012/0425.jsp.

Data Published in *Journal of Controlled Release* Demonstrate Flexibility of Accurins® to Encapsulate a Broad Range of Physically and Chemically Diverse Payloads with High Encapsulation Efficiency and Tunable Release Kinetics

Business Wire: May 10, 2016 – CAMBRIDGE, MA, U.S.A. – BIND Therapeutics, Inc. (NASDAQ: BIND), a biotechnology company developing targeted and programmable therapeutics called Accurins®, today announced the publication of detailed methods for its hydrophobic ion pairing (HIP) approach that can be applied to a wide range of ionizable molecules, greatly increasing the diversity of payloads that can be encapsulated in Accurins®. Previous data demonstrated the potential of Accurins® to deliver the aurora

B kinase inhibitor AZD2811 to tumor sites, and in this publication, researchers from BIND Therapeutics and AstraZeneca describe the preparation of nanoparticles encapsulating AZD2811 in detail and characterize their pharmacokinetics, tolerability, and mechanisms of tumor growth inhibition in preclinical models. The data are published in the May 10, 2016, issue of the *Journal of Controlled Release*.

“In addition to the aurora B kinase inhibitor AZD2811, the HIP approach can be applied to additional therapeutic payloads with the Accurins® platform,” said Jonathan Yingling, PhD, chief scientific officer at BIND Therapeutics. “Highly charged molecules, such as oligonucleotides, and small molecules with therapeutic potential but where development has been constrained by on-target systemic toxicities, can now be optimized for controlled release in diseased tissue with our HIP technology. When coupled with the targeting ligand component of Accurins® to elicit a biological response and enhance disease tissue accumulation, powerful therapeutic synergies can be created within a single particle.”

In the paper titled “A Novel *In Situ* Hydrophobic Ion Pairing Formulation Strategy for Clinical Product Selection of a Nanoparticle Drug Delivery System,” researchers describe a technique using counterions of varying physicochemical properties to optimize AZD2811 drug loading and release kinetics in Accurins® without changing the chemical structure of the active pharmaceutical ingredient (API) or properties of the polymer that make up the particle. In addition to describing the production and characteristics of a library of AZD2811 formulations using hydrophobic ion pairing, the article also provides preclinical efficacy and tolerability data for AZD2811 as well as detailed pharmaceutical characterization and mechanistic studies related to the HIP approach. AZD2811 is currently being evaluated in a phase 1 clinical trial in patients with solid tumors.

“Utilising the HIP approach, the drug loading and release kinetics of AZD2811 could be optimised to improve the therapeutic index of an important candidate drug, enable practical dosing in the clinic, and further clinical development in oncology, said Marianne Ashford, principal scientist in drug targeting, pharmaceutical sciences at AstraZeneca.

“As we focus on leveraging the unique characteristics of Accurins® to create novel ligand–payload combinations, their ability to encapsulate and control the release kinetics of diverse payloads will play a critical role,” said Andrew Hirsch, BIND’s president and chief executive officer. “This article highlights BIND’s deep expertise in nanomedicine development and our ability to work with collaborators like AstraZeneca to develop new therapies with the capabilities of our Accurins® platform. These methods provide a clear view of the broad potential of our technology for new applications that we are leveraging to accelerate our innovative medicine portfolio.”

BIND Therapeutics is a biotechnology company developing novel targeted therapeutics, primarily for the treatment of cancer. BIND’S product candidates are based on proprietary polymeric nanoparticles called Accurins®, which are engineered to target specific cells and tissues in the body at sites of disease. BIND is developing Accurins® with three different therapeutic objectives, both through internal research programs and with collaborators: innovative medicines; enabling potent pathway inhibitors; and differentiated efficacy with approved drugs. BIND’s internal discovery efforts are focused on designing oligonucleotide and immune-oncology-based Accurins®.

BIND has announced ongoing collaborations with Pfizer Inc., AstraZeneca AB, F. Hoffmann-La Roche Ltd., Merck & Co., or Merck (known as Merck Sharp & Dohme outside the United States and Canada), Macrophage Therapeutics (a subsidiary of Navidea Biopharmaceuticals), Synergy Pharmaceuticals, PeptiDream, and Affilogic to develop Accurins® based on their proprietary therapeutic payloads and/or targeting ligands. BIND’s collaboration with AstraZeneca has resulted in the aurora B kinase inhibitor Accurin AZD2811, which became the second Accurin candidate to enter clinical development. BIND’s collaboration with Pfizer has resulted in the selection of an Accurin candidate that is entering IND-enabling studies. For more information, please visit the company’s web site at www.bindtherapeutics.com.

PureTech Launches “Alivio Therapeutics” and Advances Novel Approach for Treating Inflammatory Disease

Business Wire: May 10, 2016 – BOSTON, MA, U.S.A. – PureTech Health plc (“PureTech,” LSE: PRTC), a cross-disciplinary healthcare company tackling fundamental healthcare needs, today announced the launch of Alivio Therapeutics, which is developing a novel technology for the targeted treatment of inflammatory disorders. The technology is based on an innovative hydrogel material that is designed to adhere to and deliver drugs to inflamed tissue based on the degree of inflammation (e.g., more drug is released at a site with greater inflammation). This approach may help overcome major technical challenges in the field, enabling new therapies that have the potential to address multiple acute and chronic inflammatory disorders. The technology was jointly developed by Jeff Karp, PhD, Alivio cofounder and associate professor at Brigham and Women’s Hospital (BWH), Harvard Medical School, and Alivio cofounder and PureTech Health nonexecutive director and Scientific Advisory Board member Robert Langer, ScD, David H. Koch Institute Professor at the Massachusetts Institute of Technology (MIT).

“There are dozens of diseases where inflammation plays a central role, and patients and their doctors are looking for better, longer-lasting treatments that offer relief,” said Michael B. Brenner, MD, Alivio Scientific Advisory Board member and chief of the Division of Rheumatology, Immunology and Allergy, BWH. “We are hopeful that the development of new technologies for delivering and sustaining treatment to inflamed tissue will allow us to manage chronic and acute inflammation with more precision and control.”

Current therapeutic options, such as systemic steroids and immunosuppression, can fail to adequately control disease and may have significant side effects. Furthermore, targeting newly discovered mechanisms of inflammation has historically been difficult due to off-target effects and toxicity. Alivio seeks to overcome these limitations through a novel “smart adhere and release” drug delivery system. This proprietary technology is designed to adhere to inflamed tissue and deliver anti-inflammatory medication based on the levels of inflammation in that tissue. This has the potential to maximize treatment efficacy while minimizing the risks associated with drug exposure to healthy tissues and may enable new, disease-modifying drugs. The technology has been tested in multiple animal models and published in top peer-reviewed journals, including twice in the American Association for the Advancement of Science’s journal, *Science Translational Medicine*. The technology is versatile and is designed to accommodate payloads including small molecules and biologics, and it has been the subject of multiple patent filings.

“What differentiates this technology is its potential to safely adhere to inflamed tissue while controlling drug release based on the amount of inflammation,” said Dr. Robert Langer. “These unique properties hold promise to change the way inflammatory disease is treated in a variety of indications.”

Alivio was cofounded by PureTech Health and a group of the world’s leading experts in biomaterials and immunology. The company’s founding team and advisors include:

- Jeff Karp, PhD—Alivio cofounder and associate professor at BWH, Harvard Medical School; principal faculty at the Harvard Stem Cell Institute; affiliate faculty at the Broad Institute and at the Harvard-MIT Division of Health Sciences and Technology; principal investigator, Karp Lab; published 100 peer-reviewed papers; has 65 issued or pending patents; recognized by *The Boston Business Journal* as a Champion in Healthcare Innovation and by MIT’s *Technology Review Magazine* (TR35) as one of the top innovators in the world.
- Robert Langer, ScD—Alivio cofounder and member of the Alivio Board of Directors and cofounder and nonexecutive director at PureTech Health; member of PureTech’s Scientific Advisory Board; David H. Koch Institute Professor at MIT; previously served as a member and Chair of the United States (U.S.) Food and Drug Administration’s SCIENCE Board; has over 1,100 patents worldwide that have been licensed or sublicensed to over 300 pharmaceutical, chemical, biotechnology, and medical device companies and over 1,350 publications in peer-reviewed journals.
- Michael B. Brenner, MD—Alivio Scientific Advisory Board member and Theodore B. Bayles Professor of Medicine at Harvard Medical School; chief of the Division of Rheumatology, Immunology and Allergy at BWH; made seminal discoveries in the field of antigen presentation and elucidated key mechanisms of disease in arthritis; was the scientific cofounder of Adheron Therapeutics (acquired by Roche); was elected member of the U.S. National Academy of Science; published more than 200 peer-reviewed papers.
- Ivana Magovcevic-Liebisch, PhD, JD—director, Alivio Board of Directors and senior vice president and head of global business development at Teva Pharmaceuticals; responsible for the execution of transactions identified by Teva’s research and development, global franchises, and U.S. specialty teams, including the licensing of commercial products, drug candidates, and technologies; formerly executive vice president and chief operating officer of Dyax Corporation, which was acquired by Shire Pharmaceuticals for ~\$5.9 billion; formerly director of intellectual property and patent counsel for Transkaryotic Therapies, Inc.; Applied Genetic Technologies Corporation board member.
- Ulrich H. von Andrian, MD, PhD—Alivio Scientific Advisory Board member and Mallinckrodt Professor of Immunopathology at Harvard Medical School; pioneered microscopy techniques that shaped our current understanding of how immune cells target and adhere to inflamed tissue; has published more than 200 peer-reviewed papers.
- Ralph Weissleder, MD, PhD—Alivio Scientific Advisory Board member and Thrall Professor of Radiology and Systems Biology at Harvard Medical School; director of the Center for Systems Biology at Massachusetts General Hospital; pioneered the clinical translation of various nanomaterials and imaging tools; has published more than 800 peer-reviewed papers; winner of the J. Taylor International Prize in Medicine; winner of the Society for Molecular Imaging Lifetime Achievement Award; member of the U.S. National Academy of Medicine, the American Academy of Arts and Sciences, and the German National Academy of Sciences (Leopoldina).

“PureTech is excited to be advancing this important technology, invented by Jeff Karp and Bob Langer, and to be working with our extended team of experts to launch Alivio Therapeutics,” said Daphne Zohar, cofounder and chief executive officer of PureTech Health. “There is a tremendous unmet need in inflammatory disease, so we look forward to progressing this platform, which has the potential to deliver drugs to inflammation in a new and meaningful way.”

Alivio Therapeutics is developing a novel technology for the targeted treatment of chronic and acute inflammatory disorders. Alivio is advancing its proprietary hydrogel technology, which is designed to adhere to inflamed tissue and delivers medication based on the levels of inflammation, potentially enabling improved properties while minimizing exposure to healthy tissue and other systemic side effects. Founded by PureTech Health along with several of the world’s leading experts in biomaterials and immunology, Alivio seeks to provide a solution to the dozens of conditions where inflammation is a central part of the underlying disease pathology, but targeted and effective treatment options are lacking.

PureTech Health plc (PRTC.L) owns approximately 92% of the company on a diluted basis as of December 31, 2015. This calculation includes issued and outstanding shares as well as options to purchase shares and written commitments to issue shares or options, but excludes unallocated shares authorized to be issued pursuant to equity incentive plans.

Olivo Labs Scientists Develop Novel Polymer That Replicates Young Skin

Business Wire: May 9, 2016 – CAMBRIDGE, MA, U.S.A. – Olivo Labs, the pioneering company formed to address unmet needs in the dermatological field through proprietary biomaterials technology, today announced that scientists from its lab joined together with others to publish a paper describing a novel polymer platform in *Nature Materials*. The skin-conforming silicone-based polymer has mechanical properties matching that of youthful skin while enabling additional designs in other properties such as serving as a barrier protection to minimize water loss, creating opportunities in both the aesthetic and medical markets, particularly in the area of drug delivery.

The publication, “An Elastic Second Skin,” comes after more than five years of research in which the scientific research team tested more than 100 different polymers with the goal of replicating healthy skin. The silicone-based material (XPL) upon which the Olivo platform is built can now be engineered to adjust for flexibility, elasticity, breathability, invisibility, and water resistance. Ultimately, XPL could be used to treat skin conditions such as eczema and other dermatitis and to provide long-term sun protection from UV by incorporating SPF ingredients.

“Developing a second skin that is invisible, comfortable and effective in holding in water and potentially other materials presents many different challenges, which we are now able to address,” said Dr. Robert Langer, Olivo cofounder, MIT Institute Professor, and corresponding author of the paper. “We are extremely excited about the opportunities that are presented as a result of this work and look forward to further developing these materials to better treat patients who suffer from a variety of skin conditions.”

In the publication, researchers describe studies performed on humans to test the material’s effectiveness in terms of wearability, prevention of water loss, and safety. In wearability, the XPL material outperformed two commercial wound dressings with respect to flexibility, elasticity, thickness, and visibility. In moisturization (hydration) and water loss, XPL exhibited statistically less water loss and more skin hydration than high-end commercial moisturizers. Additionally, no skin irritation was observed in these tests.

“This ‘skin conforming’ platform brings with it transport properties that have significant promise to treat underlying conditions,” said Dr. Rox Anderson, Harvard Professor, Olivo cofounder, and dermatologist at Massachusetts General Hospital. “For eczema or sun protection as examples, this second skin platform can then serve as a reservoir for control-release transdermal drug delivery or SPF ingredients, a possibility we are currently pursuing in our lab.”

The study was published today as an advance online publication on the *Nature Materials* website. Authors include Betty Yu, former vice president at Living Proof; Robert Langer, Institute Professor, MIT; Daniel Anderson, associate professor, MIT; Rox Anderson, MGH; Barbara Gilchrest, MGH; Fernanda Sakamoto, MGH; Soo-Young Kang, Living Proof; Morgan Pilkenton and Alpesh Patel, formerly of Living Proof; and Ariya Akthakul, Nithin Ramadurai, and Amir Nashat of Olivo Laboratories.

Olivo Laboratories was founded to target unmet needs in the dermatological field and provide solutions to skin-related medical conditions through proprietary biomaterials technologies. Spun out of Living Proof, Olivo Labs’ lead technology, the XPL platform, was developed in collaboration with Rox Anderson at the Wellman Center (Harvard-MGH), Bob Langer and Dan Anderson at Langer Lab (MIT), and Polaris Partners. The company seeks to create benchmark solutions through perfectly engineered products with a focus on medical and cosmetic problems.

Juniper Pharmaceuticals Announces Publication of Phase 1 Study Demonstrating Ability of Its Proprietary Intravaginal Ring to Deliver Large Molecules

PRNewswire: May 5, 2016 – BOSTON, MA, U.S.A. – Juniper Pharmaceuticals, Inc. (Nasdaq: JNP) (“Juniper” or the “company”), a women’s health therapeutics company, today announced that the *Journal of Controlled Release* has published the results of the first proof-of-concept study to explore the ability of Juniper’s intravaginal ring (“IVR”) to successfully deliver larger molecules, including peptides and proteins. The article reports that the unique technology of Juniper’s IVR differs from all of the five commercially available transvaginal rings. The abstract is available online at www.ncbi.nlm.nih.gov/pubmed/27130696. The *Journal of Controlled Release* has a current impact factor of 7.633, making it one of the most influential journals in the pharmaceuticals, biomaterials, and drug delivery fields.

“Therapies based on peptides are notoriously difficult to deliver and typically cannot be taken orally,” said principal investigator Alexa B. Kimball, MD, MPH, Massachusetts General Hospital and Harvard Medical School. “This study demonstrates the potential of a new delivery route for peptide therapeutics for women. To further explore transvaginal absorption capabilities, future studies will need to examine larger molecules and the administration of these molecules for longer periods of time and in larger numbers of women.”

The publication, “A Novel Approach to Administration of Peptides in Women: Systemic Absorption of a GnRH Agonist via Transvaginal Ring Delivery System,” explored the ability of Juniper’s IVR to deliver the nine amino acid peptide leuprolide, a gonadotropin releasing hormone agonist (GnRHa), which is sold commercially as an injectable under the brand names Eligard and Lupron for the treatment of precocious puberty, prostate cancer, infertility, fibroids, and endometriosis.

In this clinical trial, six normal healthy female volunteers underwent administration of 18 or 36 mg of leuprolide via Juniper’s novel ethylene vinyl acetate intravaginal ring drug delivery system. Consistent with the biologic activity representative of the leuprolide entering the circulation, serum levels rose within 8 h following insertion and was dose dependent. GnRHa biological activity was validated by secretion of gonadotropins and sex steroids.

These results demonstrate that the non-keratinized vaginal epithelium permits a rapid absorption of a biologically active peptide, and that there is significant potential for a novel transvaginal drug delivery system to deliver peptides and possibly other macromolecules, such as proteins, CRISPR therapeutics, siRNA, mRNA, and monoclonal antibodies, therapeutically.

“A self-administered vaginal ring provides patients with a simplified drug delivery system and should improve compliance and therefore treatment effectiveness,” said Bridget A. Martell, MA, MD, chief medical officer of Juniper Pharmaceuticals.

Coauthors of the paper include renowned scientists Robert Langer, ScD, from the Massachusetts Institute of Technology, William F. Crowley, MD, from Massachusetts General Hospital and Harvard Medical School, and Eyal S. Ron, PhD, who is now chief technology officer of Gelesis; each contributed to the development of the technology.

Peptides cannot typically be given orally because they are broken down in the stomach before they are readily absorbed. While the skin is an attractive way to deliver medications, its superb intrinsic barrier function often makes this route untenable, especially for larger peptides and proteins, and can be a barrier to compliance for some patients since transdermal patches need to be changed more than once weekly. The vaginal epithelium, in contrast, is not keratinized and can allow absorption of other molecules. Juniper’s IVR technology also allows sustained delivery over time—from weeks to months. In addition, this vaginal ring can hold one to two orders of magnitude more drug than transdermal patches, greatly expanding the number and types of drugs that can be delivered and extending the duration of use from a single dose.

Juniper Pharmaceuticals’ novel intravaginal ring (“IVR”) technology leverages a pathway unique to women, the highly vascular and non-keratinized tissue of the vaginal wall. Due to its unique polymer composition and segmentation capability, Juniper’s IVR is the only single ring that has the ability to allow dosing of small and large molecular weights of multiple drugs at multiple release rates and at multiple dosages. The IVR technology allows delivery of a range of molecules of various molecular weights including lipophilic and lipophobic molecules, which may offer the opportunity for this delivery system to be used for a range of therapeutics. The company expects to file an Investigational New Drug (“IND”) application for JNP-0101, its oxybutynin IVR candidate to treat overactive bladder in women, in the second half of 2016.

Juniper Pharmaceuticals, Inc., is focused on developing therapeutics that address unmet medical needs in women’s health. The company is advancing a pipeline of proprietary product candidates that leverage novel intravaginal drug delivery technologies. Juniper’s

commercial product, CRINONE® 8% (progesterone gel), is marketed by Merck KGaA, Darmstadt, Germany, in over 90 countries worldwide and by Allergan, Inc., in the United States. Please visit www.juniperpharma.com for more information.

Pursuit Vascular Honored as Medical Design Excellence Awards Finalist

Business Wire: May 3, 2016 – MAPLE GROVE, MN, U.S.A. – Pursuit Vascular announced today that its ClearGuard HD antimicrobial barrier cap has been selected as a finalist in the “Drug-Delivery Devices and Combination Products” category of the prestigious 19th Annual Medical Design Excellence Awards (MDEA) competition. Finalists were officially announced in the May issue of *Medical Device and Diagnostic Industry* magazine.

The prevalence of hemodialysis catheters remains high, and despite current infection control procedures results in costly and potentially deadly catheter-related bloodstream infections. The new ClearGuard HD antimicrobial barrier cap is the first and only device cleared for sale in the United States that kills infection-causing bacteria inside a long-term hemodialysis catheter. The elegant design is simple to use yet highly effective, clinically proven to substantially reduce both bloodstream infections and hospitalizations. Feedback from nurses and technicians in outpatient dialysis clinics has been outstanding, and the intuitive design may even enable more home-based dialysis and patient self-care in the future.

The MDEA is the medical technology industry’s premier design competition, and its panel of third-party jurors are committed to searching worldwide for the highest caliber medical devices that save lives, improve patient healthcare, and transform medical technology. Entries are judged by an impartial panel of experts, including practicing doctors, nurses, and technicians as well as industrial designers, engineers, manufacturers, and human factors experts.

The 2016 MDEA juror panel selected the ClearGuard HD antimicrobial barrier cap for its design and engineering innovation; function and user-related innovation; patient benefits; business benefits; and overall benefit to the healthcare system.

“We are thrilled for the ClearGuard HD antimicrobial barrier cap to be recognized as a finalist in the prestigious MDEA awards program,” said Doug Killion, president and CEO of Pursuit Vascular. “Our novel ClearGuard technology platform is playing an important role in reducing infections and keeping patients out of the hospital, which are all critical drivers as we enter an era of value-based care.”

Winners will be revealed at the 2016 MDEA Awards Ceremony being held Tuesday, June 14, 2016, in conjunction with the MD&M East event at the Jacob K. Javits Convention Center in New York City.

The ClearGuard HD antimicrobial barrier cap is the first and only device cleared for sale in the United States that kills infection-causing bacteria inside a long-term hemodialysis catheter, triggering the creation of new product code (PEH) by the Food and Drug Administration (FDA). This simple yet revolutionary single-use device is protected by five issued U.S. patents, and several other U.S. and international patent applications are pending. For more information visit www.clearguardhd.com.

Headquartered in Maple Grove, Minnesota, Pursuit Vascular, Inc., is developing a family of innovative single-use products designed to protect patients from acquiring life-threatening infections associated with long-term catheter and port use, while reducing the cost of healthcare. For more information, visit www.pursuitvascular.com.

April

3M Unveils Intelligent Inhaler Designed to Help Control Spiraling Costs of Respiratory Disease

Business Wire: April 19, 2016 – ST. PAUL, MN, U.S.A. – Research shows that an estimated 334 million people have asthma worldwide, and 65 million people have moderate to severe COPD—a number that is expected to rise 24% by the year 2034 to make COPD the world’s third leading cause of death. As cases increase, driven by the aging population, hospitals and care providers continue to see low levels of adherence and poor and inconsistent competence using current treatment devices. This has led to suboptimal outcomes and higher rates of hospital admissions. Answering the need for a solution to device misuse and adherence issues, 3M Drug Delivery Systems introduces the 3M™ Intelligent Control Inhaler, an intuitive, fully integrated device that delivers accurate doses to patients, while providing on-screen instructions for use and feedback to the patient and health care provider via an app.

“Providing an effective and intuitive delivery method for respiratory disease treatment is critical to patients, health care providers, and payers alike,” said Louise Righton, global marketing operations manager, 3M Drug Delivery Systems. “Poor technique in using an inhaler, coupled with the challenges of getting patients to adhere to their medication protocols, can lead to exacerbations, increased use

of health care resources, and ultimately, a burden on health care systems. By increasing competence and adherence, we can realize better patient outcomes and reduce health care costs.”

The 3M Intelligent Control Inhaler provides a number of unique features that offer opportunities to improve outcomes by reducing patient variability and errors and providing data on use to health care providers and payers:

- **Controlled inspiration:** a combination of breath actuation with innovative technology to control inspiratory flow rate significantly reduces errors in technique, and results in a much higher level of consistency of drug delivery between breaths and between patients.
- **Integrated patient instructions:** the inhaler’s patient-proof design gives patients confidence to use the inhaler correctly and helps eliminate critical errors in use, as well as minimizing the resources dedicated to training patients in correct inhalation technique.
- **Fully integrated device:** the dose is registered when the patient correctly inhales medication rather than on actuation of the device, delivering greater accuracy of information for the patient and cost savings for health care providers who can avoid unnecessary switches and treatment escalation.
- **Capture of inspiration data:** the inhaler utilizes a data management platform to record not only device usage but also inspiration profiles to help monitor disease progression, further supporting informed treatment decisions.

The device will be developed in partnership with a pharmaceutical company and is expected to be in wide use by the end of the decade.

“We’ve done a tremendous amount of research during the development of this technology with patients, health care providers, and payers,” said Dr. Steven Wick, technical director, 3M Drug Delivery Systems. “With 60 years of experience in inhalation technologies and 30 years in health information systems, 3M is uniquely qualified to bring forth a solution that is a definitive win for each of these stakeholders. Nothing has worked to improve inhaler technique over the past 25 years—and here we have a connected device to improve both competence AND adherence. The need for a smarter solution has never been greater, and 3M intends to put greater control of respiratory disease into the hands of patients, health care providers, and payers.”

For more information on the 3M Intelligent Control Inhaler, call 1.800.643.8086 (U.S.A.) or 44 1509 613034 (United Kingdom).

3M Drug Delivery Systems partners with pharmaceutical and biotech companies to develop and manufacture pharmaceutical products using 3M’s inhalation, transdermal, or microneedle drug delivery technology. 3M offers a full range of feasibility, development, and manufacturing capabilities to help bring products to market. Regulatory expertise, quality assurance, operations, marketed product support, and other in-house resources are available for each step of the development and commercialization process. For more information, please visit www.3M.com/dds or call 1.800.643.8086.

Transdermal Delivery Solutions Announces Regulatory Approval of Clinical Trials Commencement of Testagen® Topical Testosterone HypoSpray®

Business Wire: April 19, 2016 – PALM BEACH GARDENS, FL, U.S.A. – Transdermal Delivery Solutions Corporation (TDSC), www.TDSC.us, announced today the receipt of its releases to begin its pivotal phase of clinical trials. The British National Health Service (NHS) ethics filings (IRAS) and approval of clinical trial applications (CTAs) for TDSC’s investigational medical product dossier on Hormone Replacement Technologies’ Testagen® HypoSpray® were filed in November, 2015. NHS Ethics reviewed the protocols together on December 16, 2015, and the clinical trial applications were then finalized in mid-February and filed with the Medicine and Health Products Review Authority (MHRA) for their final review and approval, which is provided in the notices of acceptance of amended request received today.

“We are pleased that NHS Ethics and MHRA have responded so quickly to move us forward toward this next critical milestone. We expect to initiate patient screening within a few weeks,” said Kenneth Kirby, president of TDSC. “As with any drug delivery FDA-approval process, it’s been a long road of regulatory channels over the course of its development, complicated by having to repeat the process in the United Kingdom under EMEA protocols as well. It’s an exciting milestone to reach in this final stage of validating the Testagen® Testosterone HypoSpray®, which we expect to outperform the competition.”

Prof. Shern Chew and faculty from The London Clinic Advanced Therapies Centre will perform the clinical trials. Scientific advisors Prof. Richard Langford, Prof. Arthur Tucker, Prof. Atholl Johnston, and Prof. Howard Maibach of UC San Francisco will audit and oversee the research. “We are pleased and honored to have the commitment and sterling clinical input of The London Clinic as well as

Prof. Tucker, Dr. Enrico Pagani, and the team from Seahorse Scientific Services who are acting as our U.K. sponsor for the studies,” said Kirby.

These initial studies in patients will establish the ideal dose for following studies and validate earlier research that established HypoSpray technology’s greatly reduced potential for inadvertent transference to others. These studies should be completed over the next 3–4 month period.

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

Low testosterone or “Low T,” also known as hypogonadism, is a condition in men characterized by the body’s failure to produce normal amounts of the hormone testosterone, a male sex hormone produced by the testes. Low T affects nearly 14 million men in the United States; yet only 9% (1.3 million) of men diagnosed with Low T are receiving treatment for the condition. Symptoms associated with Low T include erectile dysfunction and decreased sexual desire, fatigue, loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis.

TDSC is committed to advancing the science of transdermal drug delivery using its patented spray-on delivery system. TDSC’s proprietary system enables medications to be delivered directly through the skin, for systemic or localized application, utilizing its rapid acting, patchless, spray-on technology. The company’s technology is flexible enough to be applicable to a very wide range of compounds up to small peptides for pharmaceutical or cosmetic use. No other company can offer similar, consumer friendly, dosing flexible solutions. www.youtube.com/watch?v=Ff-1z1SYoF8.

HRT, Inc., is a subsidiary of TDSC that focuses on creating innovative, specific, and medically current solutions impacting hormone replacement needs: Hormone Replacement Technologies, Inc., www.HRTINC.us.

Discovery Labs Changes Name to Windtree Therapeutics, Inc. (NASDAQ: WINT)

PRNewswire: April 18, 2016 – WARRINGTON, PA, U.S.A. – Discovery Laboratories, Inc. (Nasdaq: DSCO), a biotechnology company focused on developing aerosolized KL4 surfactant therapies for respiratory diseases, today announced that it has changed its corporate name to Windtree Therapeutics, Inc., and will trade under the Nasdaq symbol “WINT” effective at market open on Tuesday, April 19, 2016.

“Today marks a new direction in the pursuit of our mission to save and improve lives, beginning with the care of the most fragile of patients—premature infants. As we look to the future, it seems only fitting that recent changes in our leadership and approach be coupled with a name and image most reflective of our laser focus on respiratory disease, our commitment to patients, and our determination to build a valuable venture,” commented Craig Fraser, chief executive officer. “We believe this rebranding effort will allow us to better convey our focus and vision for the company and for our products, as well as reflect the fresh, new direction we are taking the company.”

The name Windtree brings to mind a number of impressions that resonate strongly within the respiratory space. “Wind” signifies breath, air, and motion, while reinforcing the ideas of dynamism and change. “Tree” signifies the lungs, long life, strength, and growth. The bringing together of the two words is intended to capture the energy and character of this unique company as it begins an important new phase of its evolution.

The company has also launched a new website, www.windtreetx.com, which provides a clearer overview of its platform technologies and vision for the future. The company has also established a presence on Twitter (@Windtreetx) and other social media platforms. The company intends to use these assets along with traditional means of disclosure to increase transparency and connectivity with investors and the medical community.

Windtree’s lead product candidate is AEROSURF®, a novel, investigational drug/device product that combines the company’s proprietary KL4 surfactant and aerosolization technologies. AEROSURF is being developed to potentially reduce or eliminate the need for endotracheal intubation and mechanical ventilation in the treatment of premature infants with respiratory distress syndrome (RDS). A phase 2b clinical trial in up to 240 premature infants was initiated late last year to study AEROSURF in premature infants 26- to 32-week gestational age receiving nasal continuous positive airway pressure (nCPAP) for RDS, compared to infants receiving

nCPAP alone. The phase 2b trial is a global trial with clinical sites in North America, Europe, and Latin America. The company remains on track to complete enrollment in this trial by the end of 2016 and release top-line results in the first quarter of 2017.

Windtree Therapeutics, Inc. is a clinical-stage biotechnology company focused on developing novel surfactant therapies for respiratory diseases and other potential applications. Windtree proprietary technology platform includes a synthetic, peptide-containing surfactant (KL4 surfactant) that is structurally similar to endogenous pulmonary surfactant—and novel drug-delivery technologies being developed to enable noninvasive administration of aerosolized KL4 surfactant. Windtree is focused initially on improving the management of respiratory distress syndrome (RDS) in premature infants and believes that its proprietary technology may make it possible, over time, to develop a pipeline of KL4 surfactant product candidates to address a variety of respiratory diseases for which there are few or no approved therapies. For more information, please visit the company's website at www.windtreectx.com.

DURECT Announces FDA Acceptance of REMOXY® NDA, PDUFA Date of September 25, 2016

PRNewswire: April 12, 2016 – CUPERTINO, CA, U.S.A. – DURECT Corporation (Nasdaq: DRRX) today announced its licensee, Pain Therapeutics (Nasdaq: PTIE), has been informed by the U.S. Food and Drug Administration (FDA) that the New Drug Application (NDA) for REMOXY®, an abuse-deterrent formulation of extended-release oxycodone (CII) capsules, is sufficiently complete to permit a substantive review and that September 25, 2016, is the target action date under the Prescription Drug User Fee Act (PDUFA).

REMOXY, an investigational drug, is a unique long-acting oral formulation of oxycodone intended to manage pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Based on DURECT's ORADUR® technology, which is covered by issued patents and pending patent applications owned by us, REMOXY is designed to discourage common methods of tampering associated with prescription opioid analgesic misuse and abuse.

In December 2002, DURECT licensed to Pain Therapeutics the right to develop and commercialize on a worldwide basis REMOXY and other oral sustained release drug candidates that use the ORADUR technology and incorporate certain specified opioid compounds. DURECT is also reimbursed for formulation and other work performed under its agreement with Pain Therapeutics, will receive additional payments if certain development and regulatory milestones are achieved with respect to the licensed drug candidates, and will receive royalties of between 6.0 and 11.5% of net sales if REMOXY or the other licensed drug candidates are commercialized, as well as a mark-up on DURECT's supply of key excipients used in the manufacture of the licensed drug candidates.

ORADUR is a proprietary technology designed to transform short-acting oral capsule dosage forms into sustained release oral products, with the added benefit of resisting common methods of prescription drug misuse and abuse compared to other controlled release dosage forms on the market today.

DURECT is a biopharmaceutical company focused on two areas of active drug development: new therapeutics based on its proprietary drug delivery platforms and new chemical entities derived from its epigenomic regulator program. Its drug development expertise is being applied primarily to the fields of pain management, CNS disorders, acute organ injury, and metabolic diseases such as NAFLD/NASH. DURECT's proprietary oral, transdermal, and injectable depot delivery technologies enable new indications and superior clinical/commercial attributes such as improved abuse deterrence, convenience, adherence, efficacy, and safety for small molecule and biologic drugs. Late-stage development programs of this nature include POSIMIR™ (SABER®-bupivacaine) and REMOXY® (ORADUR®-oxycodone). DURECT's epigenomic regulator program includes the lead molecule DUR-928 in phase 1 development. DUR-928 is an endogenous small molecule that modulates lipid homeostasis, inflammation, and cell survival. For more information, please visit www.durect.com.

Intec Pharma Expands Intellectual Property for AP-CDLD with Patent in South Korea

PRNewswire: April 6, 2016 – JERUSALEM, Israel – Intec Pharma Ltd. (NASDAQ: NTEC) (TASE: INTP), a clinical-stage biopharmaceutical company focused on developing drugs based on its proprietary Accordion Pill platform technology, today announced that the company has been informed that the Korean Intellectual Property Office granted a South Korean patent to the company's patent application for an Accordion Pill containing certain drugs, including the combination carbidopa and levodopa. The patent, granted under No. 10-1601649, is titled "Carbidopa / Levodopa Gastroretentive Drug Delivery" and is currently scheduled to remain in force until April 17, 2029. The patent belongs to the company's IN-7 patent family, which pertains to the combination of certain drugs with the Accordion Pill.

Zeev Weiss, CEO of Intec Pharma, said: "The approval of this new South Korean patent is an important step for our company in extending the intellectual property protection, and potential future market, for our leading product candidate, the Accordion Pill Carbidopa/Levodopa, beyond the United States, South Africa, and Israel."

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 induced ulcers.

March

Blue-Emu® to Extend Product Line to Include First OTC Lidocaine Pain Relief Patch Lidocare™

PRNewswire: March 28, 2016 – BRISTOL, TN, U.S.A. – The makers of Blue-Emu® announced today the launch of Lidocare™: the first lidocaine patch available over the counter and the ONLY lidocaine patch that is water-free. Following the success of the Blue-Emu® line, NFI Consumer Products have formed a partnership with Prosolus, Inc., to bring a one-of-a-kind product to the OTC market.

"After the triple-digit growth Blue-Emu® has experienced, we are truly excited about continuing to provide pain relief to all of our NFI consumers through this launch," said CEO Susan Gregory.

After the successful acquisition in 2014, NFI has taken the Blue-Emu® brand from the 10th largest dollar item in its category to the number 1 dollar item and shows no signs of slowing down.

"Blue-Emu® had an exceptional consumer base when we acquired the brand; it just needed a group to add fuel to the fire to raise consumer awareness. With this new launch, our company will now have over six products at national retailers to provide our consumers with relief," said EVP of sales and marketing Benjamin Blessing.

Lidocare™ is a truly unique OTC launch; the following are a few highlights for the brand:

- National distribution at CVS and Walgreens in April/May and other retailers later in the year.
- Up to 8 hours of pain relief.
- Every patch is produced and manufactured in the United States.
- Has the maximum available lidocaine available without a prescription: 4%.
- Patent pending technology for the ONLY water-free lidocaine patch available.
- Ultra-flexible, sweat resistant, and highly durable given the lack of water.
- As with all Blue-Emu® products: odor free.

For more information, visit the Lidocare™ website at www.lidocare.com or Blue-Emu® at www.blue-emu.com. Join the #Blueemu and #Blueemu1 social conversation on Facebook and Twitter. ■