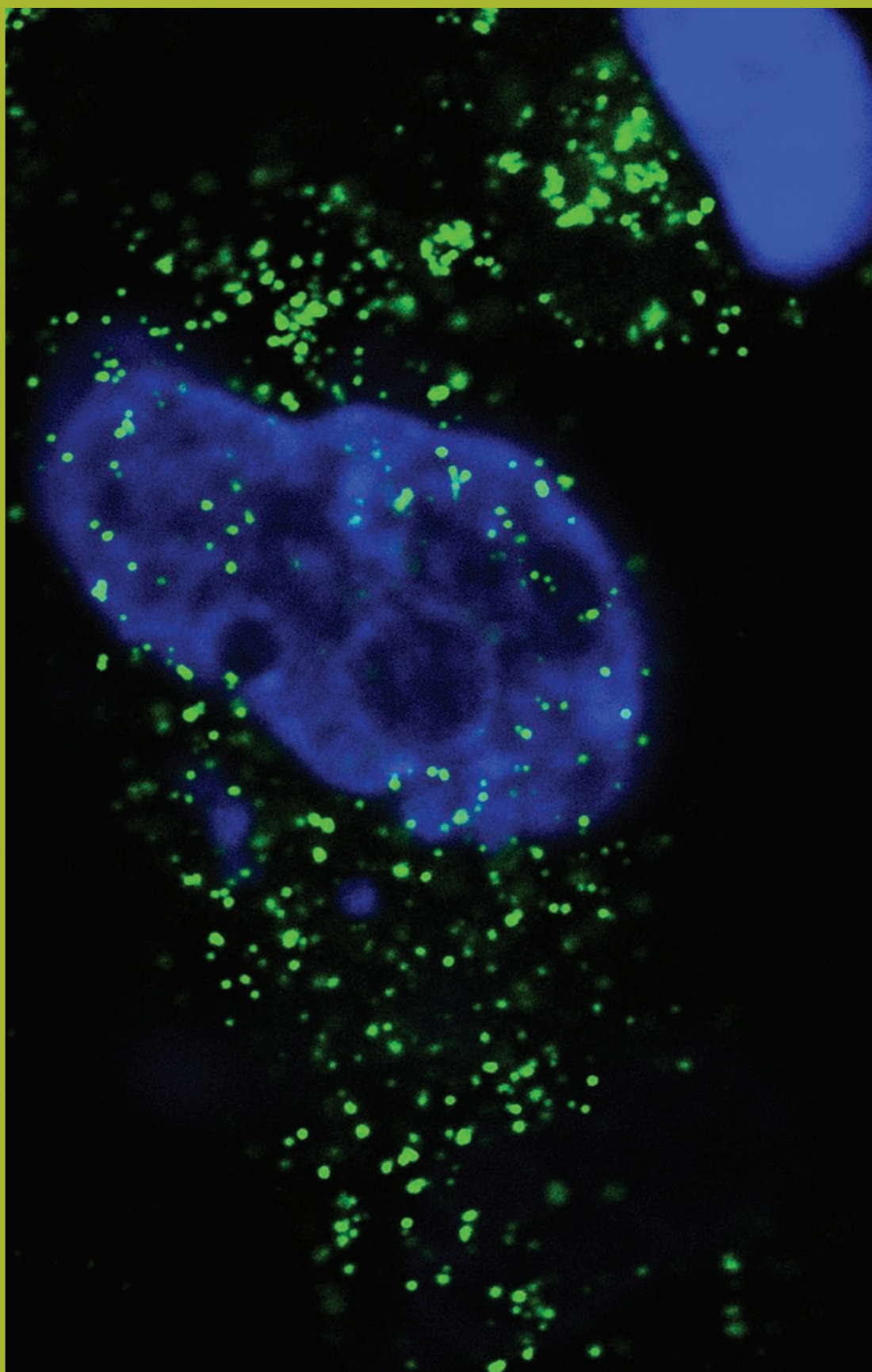
CRS Delivering Bioactives

Newsletter

A publication of the Controlled Release Society

Volume 27 • Number 6 • 2010

What's Inside



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CRS Newsletter
Delivering Bioactives

Vol. 27 • No. 6 • 2010

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The CRS Newsletter is the official newsletter of the Controlled Release Society. The newsletter is published five times annually providing scientific and technical information pertinent to the controlled release community and news about society and chapter activities. Members can receive the newsletter via mail. The newsletter may also be viewed online at www.controlledreleasesociety.org.

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Charles Frey
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Great Expectations

Thank you to all who took the time to provide feedback on questionnaires at the CRS Annual Meeting in Portland this year. Your responses provide useful program feedback to help guide continuous improvement efforts for future annual meetings. As a focal event of the Society, the success of the annual meeting in the areas of scientific content and attendance is of great importance.

I recently had the opportunity to see a questionnaire response summary. There were many positive responses, many good suggestions, and a few indications of where some improvements might be made. One pointed comment that hit me indicated concern about perceived overall presentation quality and the absence of significant technological steps forward compared with annual meetings near the turn of this century. Although I have heard such comments from other scientific meetings throughout my 29-year scientific career (wow, 29 years; from this point forward, it will remain 29 years, and I am sticking to it), I wonder if there has been a recent shift. Are scientific meetings changing? Are we losing quality to the growing efficiency burdens placed on everyone? Has the information age brought everything to our fingertips and minds such that significant advances are shared well in advance of face-to-face events? Has the lingo and speed of instant communication compromised the quality of our exchanges?

I recall reading several years ago (it might actually be nearly 20 years ago) that as we organize the findings of science and other things, the speed of knowledge assimilation is increased. Organized information can be taken in more easily in larger chunks, similar to the memorization of a number such as 568, which is easier than memorizing the separate dissociated 5, 6, and 8 digits. This falls in line with a comment I shared in a Pearls of Wisdom presentation several years ago regarding the approach to scientific truth being asymptotic: as we explain our observations in an organized manner, we may approach the truth but will never reach it. If this is true, do scientific advances eventually decrease in magnitude over the course of our spent energies? Perhaps so on a grand scale, but not likely in relation to the zoom of our current lens. Maybe the advances seen early in our careers seemed more significant on the steep learning curve of our young, ambitious minds.

If the thought has occurred to you that the quality and content of scientific meetings or societies is less than it once was, I encourage you to consider your expectations. Keep them high, but recognize that as we move forward, there is an underlying current pushing to outdo the past. Perhaps we are doing things just as well as in the past, but we expect more. Relish the pearls you find along the way—collectively they may be the great step forward. See the value of our collective Society and the relationships and motivational aspects afforded by it. Contribute where and when opportunity allows, because the information flow, the combined give and take, are the fuel of the Society.

This issue of the *CRS Newsletter* is our last for 2010, and I hope you can set aside time to read it and see what is happening in the CRS. Check out what CRS President Mark Tracy has to say; he has been bringing some good ideas to the table. Review the interview with Dr. Ronald A. Siegel. Be enlightened by the technical articles on the transfection efficacy of surface-modified polyethylenimine, nasal

From the Editor continued on page 8

Mark A. Tracy
Alnylam Inc.
Cambridge, MA, U.S.A.

Have you gone to our website lately? If not, I recommend that you check it out at www.controlledrelease.org. Led by Website Committee Chair Andy Lewis, we have begun a project to create a new website for the CRS. An updated homepage design that is now live online is just a hint of more improvements to come in 2011 as the committee carries out its work. Our vision for the new website is for it to become the primary home for the entire CRS family worldwide and to grow to be the premier web portal for the field of delivery science and technology.

To these ends, Andy and the Website Committee team, Jake Barralet, David Brayden, Biana Godin-Vilentchouk, Karl Malcolm, and Xiaoming Xu, supported by the CRS staff and Board, are working with CRS committees, groups, chapters, partners, and other stakeholders to create an updated website structure. The committee is also identifying quality vendors to work on various aspects of the project, including design, hosting, and maintenance of the new website. The new home page design that is now live online was created by the committee as a harbinger of more improvements to come and especially to highlight key CRS events and member benefits, including

- The CRS Annual Meeting & Exposition, July 30–August 3, 2011, in National Harbor, MD, U.S.A.
- The Call for Papers for our new journal, *Drug Delivery and Translational Research*
- Our highly regarded *Journal of Controlled Release*
- Our growing library of CRS Webcasts
- Our informative *CRS Newsletter*

After you review the website, please plan to attend our upcoming meetings and contribute a paper to our new journal, *Drug Delivery and Translational Research* (*DDTR*). *DDTR* is led by Editor-in-Chief Vinod Labhasetwar (Cleveland Clinic, Lerner College of Medicine) and Associate Editors Justin Hanes (Johns Hopkins University) and Kensuke Egashira (Kyushu University). *DDTR* will provide a forum for publishing research that connects basic science in drug delivery to clinical outcomes. As a complement to the *Journal of Controlled Release*, we envision that this journal will enhance our ability to promote and disseminate quality research that will facilitate the translation of delivery science to new medicines. We expect this publication will grow to be an important and essential resource for all who are interested in the interface between basic science and the clinic in the delivery field. Do not miss this unique opportunity to have your work included in the first issues of this new journal. Let's all help to make the launch of *DDTR* early in 2011 a phenomenal success!

I would like to take a moment to reflect on where we are going this year. As I said back in Portland, with recent advances, it is a special time to be in the field of delivery science and technology. The new decade that has dawned promises to be even more exciting for our field. One of my key goals is to help position the CRS not only to ride this wave but to lead it. To do this, we need to strengthen the ties with our distinguished leaders and to develop future leaders of the CRS. We will need to increase advocacy on behalf of our field as well. Toward these ends, the CRS College of Fellows and CRS Leadership Team have recently been established. Also, we need to continue to provide innovative and effective ways to bring the science to our members. Thus, we have begun new meetings and publications and are updating our website so it is better equipped to advance our science and technology. As an innovative, international organization, we need a website that reflects the sophistication of our members and our science, since the website will grow to serve as the primary home for our members worldwide and as a valuable resource for the field in general. As noted, we have begun work toward this goal. In addition, we need to update our bylaws and governance. This effort has begun, and I will talk about this process in a future column. We are also focused on maintaining and enhancing our financial strength. I hope these efforts will help bring our CRS family worldwide even closer together, help advance our science and technology, and invigorate our Society in this new decade.

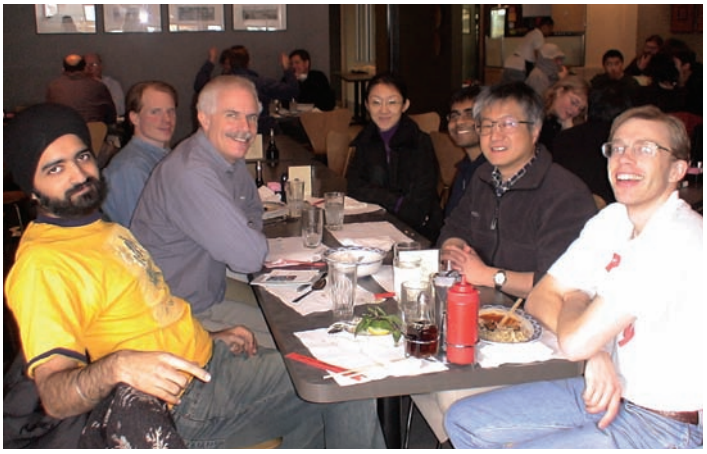
Mark A. Tracy ■

Interview with Dr. Ronald A. Siegel

Brian Kilfoyle and Bozena Michniak-Kohn, Ph.D.
Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, Piscataway, NJ, U.S.A.

Dr. Ronald A. Siegel is a professor in the College of Pharmacy at the University of Minnesota. He received his B.S. degree in mathematics from the University of Oregon (1975), his M.S. degree in electrical engineering and computer science from MIT (1979), and his Sc.D. degree in bioelectrical engineering from MIT (1984). He began his career as a research programmer and analyst at Oregon Research Institute in Eugene, OR (1969–1975), and Systems Control, Inc. in Palo Alto, CA (1975–1976), before working as a research and teaching assistant in the Departments of Electrical Engineering and Computer Science and Nutrition and Food Science at MIT in Cambridge, MA (1976–1983). During this time, Dr. Siegel also worked as a research engineer at Scientific Systems, Inc. in Cambridge, MA (1978). Upon leaving MIT, Dr. Siegel joined the Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry at the University of California at San Francisco in San Francisco, CA. While at UCSF, Dr. Siegel served as assistant professor (1984–1990), associate professor (1990–1997), professor (1997–1998), vice chair for the Department of Biopharmaceutical Sciences (1996–1998), and training grant director for the Joint UCSF/UCB Bioengineering graduate program (1996–1998). In 1998, he moved to the University of Minnesota, where he has served the Department of Pharmaceutics as professor (1998–present) and department head (1999–2009) and the Department of Biomedical Engineering as professor (2000–present).

Dr. Siegel has received numerous awards over the course of his distinguished career, only a select few of which will be highlighted here. At the beginning of his career, Dr. Siegel was awarded an NIH Predoctoral Fellowship (1978–1980), the American Association of Pharmaceutical Scientists (AAPS)/Pfizer Young Investigator Grant Award (1988), and the Controlled Release Society Young Investigator Research Award (1989), all indicating the scientific promise that Dr. Siegel showed early in his career. He has been awarded Fellow status in the American Institute for Medical and Biological Engineering (1999), the American Association of Pharmaceutical Scientists (1999), and the Controlled Release Society (2010). Dr. Siegel has also served as the president of the Controlled Release Society (1997–1998) and on the CRS Executive Committee (1996–2000). He was inducted as a CRS Fellow in 2010.



With research group at Hong Kong Noodle in Minneapolis (1996). From left: Amardeep Bhalla (grad student), Jon Urban (grad student), Dr. Siegel, Helen Hou (grad student), Siddharthya Mujumdar (grad student), Takehisa Hanawa (visiting professor), and Eric Nuxoll (post-doc).

We would like to sincerely thank Dr. Siegel for sharing his knowledge and advice with us. Now, on to the interview.…

Interview

Q ***How did your career bring you to the University of Minnesota? What are the benefits of working there?***

A I received my Sc.D. degree from MIT in 1984, working in Bob Langer's lab. I was Bob's second doctoral student and the first to go to academia. I went straight (without a post-doc) to the University of California at San Francisco in the Department of Biopharmaceutical Sciences, where I built up my career over the next 14 years. I also got involved with the joint graduate program in bioengineering between the San Francisco and Berkeley campuses. I became attracted to Minnesota because of the close proximity, literally across the street, of the basic science, engineering, and health science units, which made collaboration easier than crossing the San Francisco Bay. I was especially interested in the micro/nanofabrication facility at Minnesota, which would be essential for new areas of research that I wanted to pursue. Also, the Twin Cities offered many advantages in raising young children (who are now grown).

Q ***How has your background in mathematics, electrical engineering, and computer science led you to drug delivery systems? How has your unique background assisted you in your career?***

A Please indulge a long answer!

I started out as a math major with interest in premed. After taking chemistry and biology labs, I realized I was not cut out for medicine, and I was pleased to hear of a new field called biomedical engineering. After college, I worked for a year as a computer programmer in a company that did a lot of mathematical modeling, systems optimization, and control. I worked on projects dealing with electrical power and water distribution networks, ozone in the atmosphere, and automobile emissions. Working in control theory made me think about the relationship between drug inputs and effects. Could control engineering be helpful for drug therapy?

In the mid-1970s there were few biomedical engineering graduate programs, so I chose electrical engineering and computer science. I first got a master's degree at MIT, working in hearing research. In the process, I learned a lot about noise and random processes. I also took courses in electromagnetic field theory and biotransport and learned about techniques to solve equations similar to those encountered in diffusion. After I finished my master's and met Bob Langer, it was clear that I could use my background to solve some problems that Bob was interested in. How do proteins get released from highly reticulated porous polymer matrices? Why is the release so slow, and how can it be controlled? How could we model the complex, tortuous pathways that proteins must traverse during the release process? How did these problems relate to percolation theory, which at the time was being developed primarily by theoretical physicists but was being applied to such diverse fields as electrical conduction in composite materials and tertiary oil extraction? Stochastic computational algorithms that I developed to answer these questions were inspired by what I had learned in math and electrical engineering.

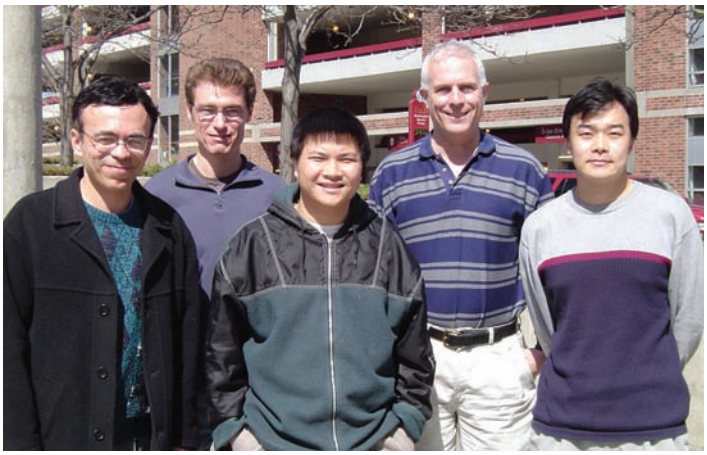
My choice of research problems has also been influenced strongly by my background. While most of my students and post-docs have been primarily experimentalists, we have typically focused away from, say, novel chemistries but oriented more toward understanding mechanical and transport behaviors of materials and constructing novel devices based on that understanding. Feedback control has been on my mind all along, and we have been investigating both closed loop and open loop controlled delivery. More about this below.

Q ***When you finished graduate school, why did you decide to stay in academia instead of pursuing a career in industry?***

A I grew up in an academic family and was familiar with many of its benefits, particularly the opportunity to travel. I also wanted to be able to choose the problems I would work on and have the opportunity to train graduate students. It is gratifying to see students develop their skills and ability to think about scientific questions. Of course, just when they become most valuable, they graduate!

Q ***What are the general research interests of your group?***

A We have been interested in the physical chemistry of stimuli-sensitive hydrogels and their potential utility in sensing and drug delivery. We started out in the 1980s looking at pH-sensitive hydrogels but turned to thermosensitive and glucose-sensitive gels in the 1990s. More recently we have become interested in hydrogel and membrane nanostructures formed by block polymers. Collaborative work addresses the integration of hydrogels with microdevices. Side interests include mathematical modeling of swelling, membrane transport, and pharmacokinetics/pharmacodynamics.



Microfabrication team (1993). From left: Prof. Babak Ziaie, Antonio Baldi (post-doc), Alex Gu (grad student), Dr. Siegel, and Ming Lei (grad student).

Q ***What is an "artificial pancreas" and how is your group approaching this work?***

A A functioning pancreas monitors glucose level in the blood and secretes insulin when blood glucose level is too high. In Type I diabetes, the pancreas loses its ability to perform this closed loop feedback function. Present insulin therapies are typified by finger sticks and injections, which do not provide good control of glucose level. An artificial pancreas is a system that would, by properly sensing glucose and delivering insulin, replace the function of a normal pancreas.

In recent decades, sophisticated wearable insulin pumps have appeared, as have implantable glucose-sensing electrodes. One form of artificial pancreas would use these two components, plus an algorithm for controlling the pump based on sensor output time series. Both components also require skin puncture, vigilance regarding cleaning, and frequent replacement of electrodes and catheter tubing. Our present goal is to produce an implantable glucose sensor which, following minor surgery and recovery, continuously monitors interstitial glucose concentration and reports it to an external radio frequency circuit by wireless interrogation. This work, in collaboration with Prof. Babak Ziaie (initially at Minnesota but now at Purdue), combines hydrogel physical chemistry with microfabrication. Briefly, glucose-sensitive swelling and shrinking of the hydrogel alters the resonant frequency of a microcircuit, which can be sensed by an external radio unit. We have already constructed such a sensor, but we need to work on its response time, specificity to glucose, and its biocompatibility.

It is also possible to use swelling and shrinking of a glucose-responsive hydrogel to gate insulin flow through a microfluidic valve, thus closing the loop and functioning like a pancreas. We have demonstrated this principle, but feel at this point that further development of the sensor needs to take priority—the sensor should be shown to work first before adding the complication of insulin delivery. However, in the process of thinking about microvalves, we have come up with

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several interesting designs that may have other applications.

Baldi, A, Gu, Y, Loftness, PE, Siegel, RA, Ziaie, B. A hydrogel actuated environmentally-sensitive microvalve for active flow control, J. Micromech. Syst. 12: 613-621 (2003).

Lei, M, Baldi, A, Nuxoll, E, Siegel, RA, Ziaie, B. A hydrogel-based implantable micromachined transponder for wireless glucose measurement, Diabetes Tech. Therap. 8: 112-122 (2006).

Baldi, A, Lei, M, Gu, Y, Siegel, RA, Ziaie, B. A microstructured silicon membrane with entrapped hydrogels for environmentally-sensitive fluid gating, Sensors Actuators B Chem. 114: 9-18 (2006).

Lei, M, Ziaie, B, Nuxoll, E, Ivan, K, Noszticzius, Z, Siegel, RA. Integration of hydrogels with hard and soft microstructures, J. Nanosci. Nanotech. 7: 780-789 (2007).

Siegel, RA, Gu, Y, Lei, M, Baldi, A, Nuxoll, EE, Ziaie, B. Hard and soft micro- and nanofabrication: An integrated approach to hydrogel based biosensing and drug delivery, J. Control. Release 141: 303-313 (2010).

Q ***Your group is also developing an implantable device for delivery of hormones. Could you please briefly discuss this work and its potential applications? What challenges exist?***

A Sexual maturation and reproductive function are controlled by rhythmic secretion of peptide hormones. For those with deficiencies in gonadotropin-releasing hormone (GnRH, aka LHRH), replacement only works if it is administered at the normal, endogenous frequency. While rhythmic intravenous GnRH pumps are available for women wishing to become pregnant, these pumps are not necessarily desirable for chronic treatment. GnRH is extremely potent, and our thought was to develop an implantable device which would automatically release small amounts of GnRH in rhythmic pulses. Taking a cue from work on oscillating chemical and biochemical reactions, we conceived a hydrogel membrane/enzyme combination which, fueled by endogenous glucose, undergoes periodic swelling/shrinking cycles. Design of this system has required understanding of hydrogel physics, feedback control theory, and nonlinear dynamics. Presently, we can report a demonstration of principle in a bench-top system, which exhibited rhythmic delivery of GnRH for up to one week. Much work has to be done regarding miniaturization, prevention of system fatigue, and adaptation to physiologically realistic conditions.

Siegel, RA, Pitt, CG. A strategy for oscillatory drug release: General scheme and simplified theory, J. Control. Release 33: 173-188 (1995).

Misra, GP, Siegel, RA. A new mode of drug delivery: Long term autonomous rhythmic hormone release across a hydrogel membrane, J. Control. Release 81: 1-6 (2002).

Dhanarajan, AP, Urban, J, Siegel, RA. A model for a hydrogel/enzyme oscillator, In, Pojman, JA, and Tran-Cong-Miyata, Q. (eds.), Nonlinear Dynamics in Polymeric Systems, ACS Symposium Ser. No. 869, ACS, Washington, DC (2003).

Mujumdar, SK, Bhalla, AS, Siegel, RA. Novel hydrogels for rhythmic pulsatile drug delivery, Macromol. Symp. 254: 338-344 (2007).

Siegel, RA. Autonomous rhythmic drug delivery systems based on chemical and biochemical oscillators, In, Borckmans, P, DeKepper, P, Khokhlov, A, Mètens, S. (eds.), Chemomechanical Instabilities in Responsive Materials, Springer, Dordrecht, Netherlands, pp175-201 (2009).

Q ***What are the key differences in the science behind the "artificial pancreas" and the implantable device to deliver hormones?***

A The sensing arm of the artificial pancreas relies on the hydrogel responding [to] changes in glucose concentration that occur in diabetes. In the rhythmic hormone delivery device, glucose acts more like a fuel source which drives oscillations in membrane permeability by a feedback instability, even when glucose concentration is essentially constant. An electronic analogy is a flashing bike light driven by a DC battery.

Q ***What is a point-of-administration mixing system, and how will it be utilized for nasal drug delivery?***

A Numerous drugs suffer from low solubility, which hinders their absorption. Formulation of drugs at supersaturating concentrations has been of interest, but such formulations are unstable and therefore difficult to store. This being the case, why not formulate at the point of administration? We are trying out this idea with diazepam, a drug used to treat epilepsy. Presently, someone experiencing or anticipating a seizure must receive diazepam iv or rectally to ensure fast action, but neither of these routes is practical or acceptable for most people. We are seeking methods to administer diazepam intranasally, using point-of-administration formulation. This requires mixing two solutions rapidly to produce supersaturated diazepam.

Hou, H, Siegel, RA. Enhanced permeation of diazepam through artificial membranes from supersaturated solutions, J. Pharm. Sci. 95: 896-905 (2006).

Ivaturi, VD, Riss, JR, Kriel, RL, Siegel, RA, Cloyd, JC. Bioavailability and tolerability of intranasal diazepam in healthy adult volunteers, Epilepsy Res. 84: 120-126 (2009).

Q ***What do you regard as the most significant achievement(s) of your scientific career thus far?***

A Demonstrating rhythmic release of hormones from a hydrogel/enzyme construct, fueled by a constant level of glucose was, in my view, the most unique thing we have done. It took the serial efforts of three very talented post-docs to achieve this result. It took some confidence (and stubbornness and tenure) to keep this work going until we were successful. I am also proud of our early work with hydrophobic pH-sensitive hydrogels and more recent work combining hydrogels and block polymers with microfabricated solid-state devices. In the modeling arena, we made some unique contributions to

the theory of time lags in membrane transport and also showed how to adapt theories from controlled release to model the behavior of reactive barrier membranes used in packaging, coatings, and environmental containment. Finally, stochastic computational techniques explored in my dissertation were adapted to other fields in which diffusion in porous media is important.

Siegel, RA, Langer, R. A new Monte Carlo approach to diffusion in constricted porous geometries, J. Coll. Interf. Sci. 109: 426-440 (1986).

Siegel, RA, Firestone, BA. pH-dependent equilibrium swelling properties of hydrophobic polyelectrolyte copolymer gels, Macromolecules 21: 3254-3259 (1988).

Siegel, RA, Falamarzian, M, Firestone, BA, Moxley, BC. pH-controlled release from hydrophobic/polyelectrolyte hydrogels, J. Control. Release 8: 179-182 (1988).

Siegel, RA. Algebraic, differential and integral relations for membranes in series and other multilaminar media: Permeabilities, solute consumption, lag times and mean first passage times, J. Phys. Chem. 95: 2556-2565 (1991).

Siegel, RA, Cussler, EL. Reactive barrier membranes: Some theoretical observations regarding the time lag and breakthrough curves, J. Membr. Sci. 229: 33-41 (2004).

Nuxoll, EE, Hillmyer, MA, Wang, R, Leighton, C, Siegel, RA. Composite block polymer-microfabricated silicon nanoporous membrane, ACS Appl. Mater. Interf. 1: 888-893 (2009).

Q ***Which scientists have played an important role in your scientific development?***

A Too many to list them all! My master's advisor, Steve Colburn, taught me how do define a research problem. Bob Langer introduced me to controlled release and exhibited enthusiasm for modeling coupled with tremendous patience as I initially fumbled around in the lab. The early days in the Langer lab were exciting, kind of like witnessing the Big Bang! A course titled "Fields, Forces and Flows, Background for Physiology," taught by Alan Grodzinsky, was valuable to my thesis work and later research. At UCSF, I was heavily influenced by Ken Dill, Dirk Stigter (deceased), and Jorge Heller (deceased), who helped me learn polymer physics and chemistry; by Frank Szoka and Richard Guy, who opened my eyes to different kinds of drug delivery; and by Lewis Sheiner (deceased), who broadened my understanding of pharmacokinetics and pharmacodynamics. Other CRS scientists who have influenced me strongly include Teruo Okano, Kazunori Kataoka, Allan Hoffman, Buddy Ratner, Yosi Kost, Nick Peppas, Henry Kopecek, and Sun Wan Kim. Outside the controlled release field, I am indebted to Ed Cussler, Toyoichi Tanaka (deceased), Yoshihito Osada, Jian Ping Gong, John Ross, Irving Epstein, and Albert Goldbeter.

Collective effort to trigger pulsatile release of sake. Some may recognize Profs. Andres Garcia (Georgia Tech) and Tejal Desai (UCSF).

Q ***If you were to give advice to a recent or soon-to-be graduate, what would it be?***

A A good dissertation experience should provide you with many of the tools you need to be a successful scientist, but it is just the beginning. When you start in an area of research, get to know the available literature, and think about what questions need to be answered. Develop areas in which your expertise is critical, even if the work you do is collaborative. Finally, try to keep abreast of what is going on in the science outside your field (by reading *Science* or *Nature*, for example).

Another piece of advice is, maintain a healthy skepticism. We don't understand things as well as it may seem! Apply this skepticism to your own results and challenge your conclusions with control experiments. Good controls often tell you more than the target experiment.

Q ***What personal attributes have allowed you to excel in your scientific career?***

A Mostly curiosity. Also, I have tried to find areas or research where my background is relatively unique.

Q ***Outside of your scientific endeavors what hobbies do you enjoy?***

A I have been playing fiddle in folk and bluegrass bands since I was in graduate school, and I have learned several styles of ethnic music. Besides the fun of performing on stage, music provides an opportunity to meet people from many walks of life. I also enjoy reading scientific biographies and books that explore the development of big ideas in science, such as evolution, molecular biology, relativity, quantum mechanics, and information theory.

Q ***Do you have any musical performances available online that we could provide a link to?***

A My band has a website: www.myspace.com/switchedatbirthgroup. *(Interviewer Note: You don't need a myspace account to check out the website. There are a handful of songs on the site that are certainly worth checking out. Dr. Siegel is featured on the fiddle in the song "Jewish Dance." An amazing performance.)*

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Q ***Where are some of your favorite places to travel both for conferences and for relaxation?***

A The annual CRS meeting is always a great venue to learn new things, see old friends, and meet new faces. My favorite meetings are relatively small gatherings dedicated to particular topics. A particular gem was a NATO conference on self-organization in materials, held in a small town in Corsica. No telephone or TV in my flat, but a gorgeous view of the Mediterranean. I have also enjoyed the hospitality of colleagues in Japan, Korea, Russia, Spain, and Hungary and have taken family trips to Israel, Italy, Japan, Greece, Romania, Hawaii, and the Caribbean.

Q ***How have you been able to balance a successful career in science with your passion for music and love of family?***

A This question of balance is frequently on the minds of young scientists contemplating research and academic careers. There is no simple answer, and I have, at times, had difficulty in striking the right balance between work and family. As conflicts arise, one needs to be alert to the effects that they have on family members and to be willing to make changes to restore balance.

Music brought me and my wife together, and it has been an important part of our family life. When the kids were little, I cut back on performing, but resumed when they got older and more independent. I hope to keep playing fiddle long after I retire. ■

From the Editor continued from page 2

delivery with chitosan-based polyelectrolyte complexes, and use of cyclodextrins for injectable delivery of poorly soluble compounds. Read about the organization, scope, and technical achievements of TNO Science and Industry in the Netherlands. Perhaps you are interested in the 14th Industrial Symposium and 5th Trade Fair on Microencapsulation that is being offered this coming March in San Antonio, TX, through CRS and the Bioencapsulation Research Group. San Antonio will be a welcome destination at that time of year.

This has been my first year contributing in an editorial capacity to the *CRS Newsletter* on behalf of the consumer and diversified product areas of controlled release. Although my work has a pharmaceutical focus, it also touches on the areas of food, nutrition, household products, agriculture, and varied other industries. I hope you can join me in applauding the efforts of the editorial volunteers and people who have been bringing this informative newsletter to you.

Keep your expectations high, and the combined efforts of you and the CRS will rise to meet them.

Chuck Frey ■

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Enhanced Transfection Efficacy of Polyethylenimine by Surface Modification with Arginine, Lysine, and Leucine

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Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow, U.K.

Introduction

The potential of gene therapy is currently limited by the lack of delivery systems able to efficiently carry therapeutic DNA to their site of action. Non-viral vectors are receiving increasing attention as gene delivery vehicles due to the limitations associated with viral vectors in terms of safety and immunogenicity. Unfortunately, their use is hampered by their lower transfection efficacy compared with viral systems. The present study investigates the possibility of improving transfection by grafting amino acids onto the surface of a non-viral gene delivery system. We chose to use the amino acids arginine, lysine, and leucine because they have been reported to enhance transportation into cells (1–3). As a model delivery system, we chose to use the polymer polyethylenimine (PEI), because it has been widely used for non-viral transfection *in vitro* and *in vivo* and combines strong DNA compaction capacity with an intrinsic endosomolytic activity known as the proton sponge effect (4–5). It is hypothesized that arginine-, lysine-, and leucine-bearing polyethylenimine would lead to improved transfection efficacy through the synergistic action of the proton sponge effect and hydrophobic interactions with the cellular membranes.

The objectives of this study, therefore, are 1) to prepare and characterize arginine-, lysine-, and leucine-bearing polyethylenimine; 2) to evaluate their transfection and therapeutic efficacies *in vitro* on the A431 human epidermoid carcinoma cell line; and 3) to evaluate their transfection efficacy *in vivo* after intravenous administration in mice bearing A431 tumours.

Experimental Methods

Amino acid coupling to PEI was performed using a cross-linking agent and characterized as previously described (6). The *in vitro* cellular uptake of the amino acid-bearing polyplexes was qualitatively evaluated by confocal microscopy on A431 cells. The transfection efficiency was investigated at different polymer/DNA weight ratios and compared with unmodified PEI and DOTAP. Cytotoxicity was determined using an MTT assay. The *in vivo* biodistribution of gene expression in mice bearing subcutaneous A431 tumours was assessed using a β-galactosidase assay.

Results and Discussion

The grafting of arginine, lysine, and leucine residues on PEI was confirmed by ^{1}H NMR, and the three amino acid-bearing polymers were fully characterized. The highest *in vitro* transfection efficacy for the three amino acid-bearing PEI polyplexes was observed at a polymer/DNA weight ratio of 20:1, although it was not significantly different from that observed at a weight ratio of 10:1 for arginine-bearing polyplex and 10:1 and 5:1 for leucine-bearing polyplex (Figure 1A). The conjugation of arginine and

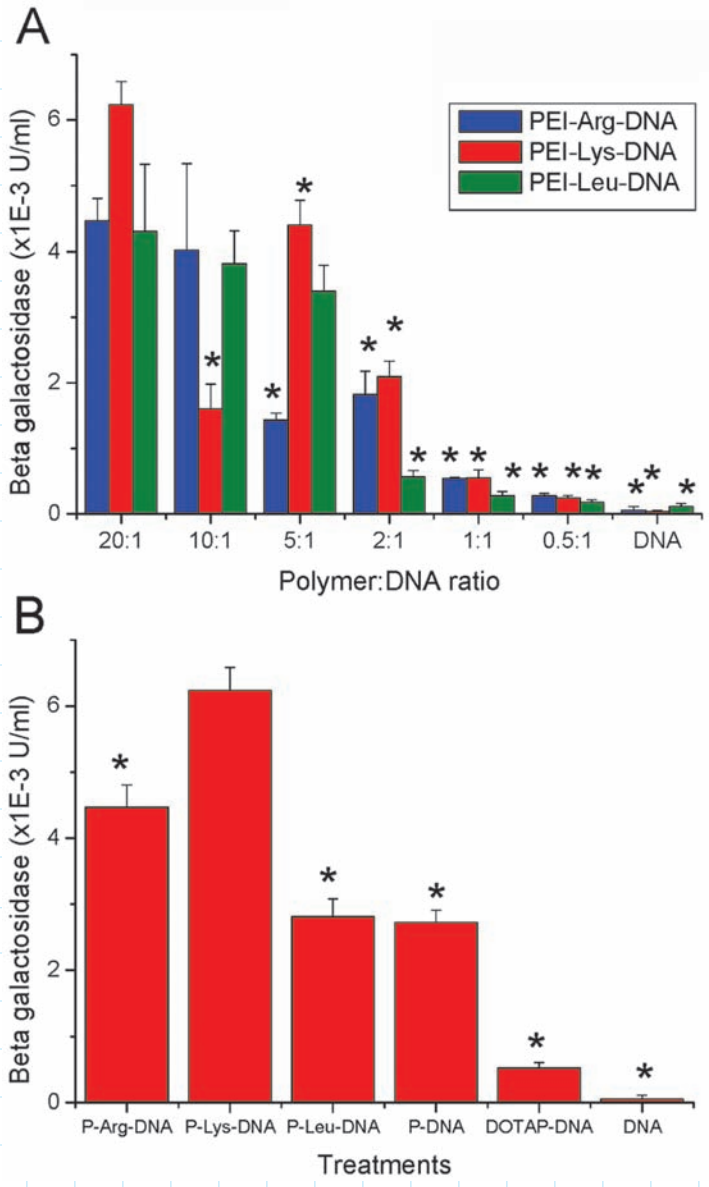

Figure 1. *Transfection efficacy of PEI-Arg, PEI-Lys, and PEI-Leu polyplexes at various polymer/DNA weight ratios (**A**) relative to DOTAP and native PEI (**B**) in A431 cells. DOTAP-DNA and PEI-DNA were dosed at their optimal carrier/DNA ratio of 5:1. Results are expressed as the mean ± SEM of three replicates (*n = 15). * *indicates* P < *0.05 versus the highest transfection ratio (**A**) or treatment (**B**).*

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lysine residues to PEI led to improved transfection compared with the native PEI and DOTAP on the tested cell line, with improvements of up to 11.7 times following treatment with lysine-bearing polyplex compared with DOTAP-DNA (Figure 1B).

The administration of a therapeutic DNA complexed with arginine-, lysine-, and leucine-bearing PEI led to improved therapeutic efficacy compared with the unmodified polymer on the cancer cell line tested, by up to 51 times (Table 1).

The uptake of Cy3-labeled DNA by A431 cells was qualitatively confirmed using confocal microscopy (Figure 2). The complexation of plasmid DNA to PEI improved DNA uptake by the cells compared with DNA solution. Co-localization of DNA in the nuclei was clearly visible after treatment with PEI-Arg polyplex. It was less pronounced in the case of the other treatments.

The intravenous *in vivo* administration of PEI-Arg, PEI-Lys, and PEI-Leu polyplexes led to a significant increase in gene expression in the tumour, with a β-galactosidase amount at least threefold higher than that obtained after treatment with unmodified PEI polyplex (18.2 ± 1.2, 20.4 ± 3.7, and 19.2 ± 3.1 mU of β-galactosidase per tumour, respectively, for PEI-Arg, PEI-Lys, and PEI-Leu polyplexes compared with 6 ± 1.8 mU of β-galactosidase per tumour for PEI polyplex) (Figure 3).

Table 1. Anti-proliferative activity of TNFα-expressing DNA complexed with PEI-Arg, PEI-Lys, PEI-Leu, and PEI in A431 cells, expressed as IC_{50} values (n = 15)

Formulation	IC_{50} (μg/mL) (mean ± SEM)
PEI-Arg-DNA	0.52 ± 0.13
PEI-Lys-DNA	0.35 ± 0.07
PEI-Leu-DNA	0.44 ± 0.16
PEI-DNA	17.86 ± 5.34
PEI-Arg	>50
PEI-Lys	>50
PEI-Leu	>50
DNA	>50

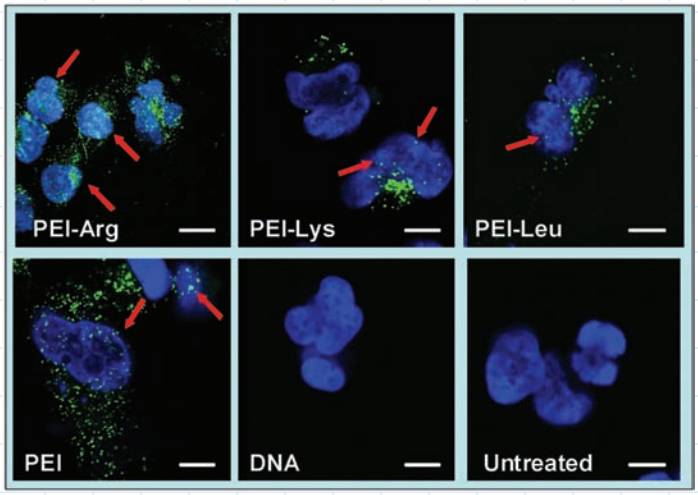

Figure 2. *Confocal microscopy imaging of the cellular uptake of Cy3-labeled DNA (6 μg/dish) either complexed with PEI-Arg, PEI-Lys, PEI-Leu, or PEI or free in solution after incubation for 24 hr with A431 cells (control: untreated cells). Blue: nuclei stained with DAPI (excitation:405-nm laser line; bandwidth: 415–491 nm); green: Cy3-labeled DNA (excitation: 453-nm laser line; bandwidth: 550–620 nm). Bar = 10 μm.*

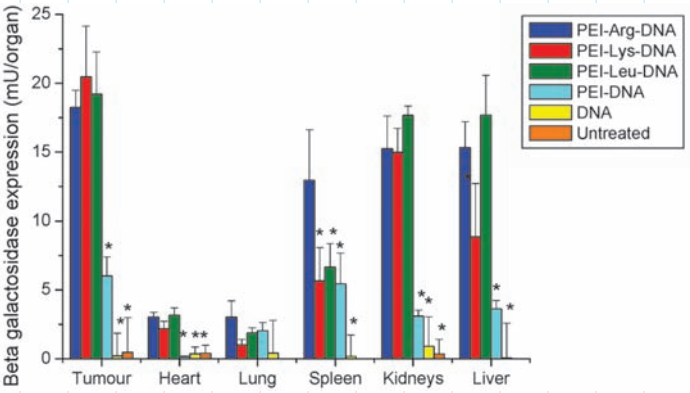

Figure 3. *Biodistribution of gene expression after a single intravenous administration of Arg-, Lys-, or Leu-bearing PEI polyplexes (50 μg of DNA administered) or unmodified PEI polyplexes (50 μg of DNA administered). Results were expressed as milliunits of* β*-galactosidase/organ (*n *= 5). * indicates* P < *0.05: highest gene expression treatment versus other treatments for each organ.*

The three amino acid-bearing PEI led to similar levels of gene expression in the tumour. The treatments were well tolerated by the mice at the administered doses. Gene expression was also increased in the kidneys (by at least fourfold) and in the liver (by approximately fivefold for PEI-Arg and PEI-Leu and twofold for PEI-Lys) after administration of amino acid-bearing PEI polyplexes. PEI-Arg polyplex also increased gene expression level in the spleen by approximately twofold compared with the other amino acid-bearing and unmodified PEI polyplexes. Gene expression within the heart and lung was weak following all treatments, reaching a maximum of 3.1 ± 0.5 mU of β-galactosidase per heart after treatment with PEI-Leu polyplex and 3 ± 1.1 mU of β-galactosidase per lung after treatment with PEI-Arg polyplex.

Conclusions

New arginine-, lysine-, and leucine-bearing PEI polymers have been prepared with the aim of improving gene expression in cancer cells. The therapeutic efficacy *in vitro* of DNA encoding TNF-α was improved when delivered with amino acid-bearing PEI, by up to 51 times compared with unmodified PEI on the A431 cell line. The intravenous *in vivo* administration of PEI-Arg, PEI-Lys, and PEI-Leu polyplexes led to improved tumour gene expression. Arginine-, lysine-, and leucine-bearing PEI polymers, thus, are promising gene delivery systems for cancer therapy.

Acknowledgments

This work was supported financially by a Ph.D. studentship from the Saudi Cultural Bureau and King Abdulaziz University (Kingdom of

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Saudi Arabia) to Hibah Aldawsari and by a University of Strathclyde (United Kingdom) New Lecturer Starter grant to Christine Dufès.

References

1. Tung, CH, Weissleder, R. Arginine containing peptides as delivery vectors, Adv. Drug. Deliv. Rev. 55: 281-294 (2003).
2. Nakanishi, M, Egushi, A, Akuta, T, Nagoshi, E, Fujita, S, Okabe, J, Senda, T, Hasegawa, M. Basic peptides as functional components of non-viral gene transfer vehicles, Curr. Prot. Pept. Sci. 4: 141-150 (2003).
3. Kim, DK, Kim, IJ, Hwang, S, Kook, JH, Lee, MC, Shin, BA, Bae, CS, Yoon, JH, Ahn, SG, Kim, SA, Kanai, Y, Endou, H, Kim, JK. System L-amino acid transporters are differently expressed in rat astrocyte and C6 glioma cells, Neurosci. Res. 50: 437-446 (2004).
4. Godbey, WT, Wu, KK, Mikos, AG. Tracking the intracellular path of poly(ethylenimine)/DNA complexes for gene delivery, Proc. Natl. Acad. Sci. USA 96: 5177-5181 (1999).
5. Nam, HY, Nam, K, Hahn, HJ, Kim, BH, Lim, HJ, Kim, HJ, Choi, JS, Park, JS. Biodegradable PAMAM ester for enhanced transfection efficiency with low cytotoxicity, Biomaterials 30: 665-673 (2009).
6. Koppu, S, Oh, YJ, Edrada-Ebel, R, Blatchford, DR, Tetley, L, Tate, RJ, Dufès, C. Tumor regression after systemic administration of a novel tumor-targeted gene delivery system carrying a therapeutic plasmid DNA, J. Control. Release 143: 215-221 (2010). ■

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Photo courtesy of National Harbor.

Chitosan-based Polyelectrolyte Complexes for Nasal Drug Delivery[1]

Barbara Luppi,[2] Federica Bigucci,[2] Angela Abruzzo,[2] Giuseppe Corace,[2] Teresa Cerchiara,[3] Andrea Bedini,[4] Santi Spampinato,[4] and Vittorio Zecchi[2]

Nasal mucoadhesive systems have been investigated with the aim of altering the pharmacokinetics of orally and parenterally administered drugs in a fashion that can enhance their pharmacologic profiles. In fact, the large surface area, porous endothelial basement membrane, and high total blood flow of the nasal mucosa ensure rapid absorption of compounds under circumvention of the hepatic first-pass metabolism (1). Moreover, the accessibility of the nasal route provides quick and easy self-medication compared with other routes, thus improving patient compliance. A major problem of nasal drug delivery is the mucociliary clearance mechanism that rapidly removes non-mucoadhesive applied dosage forms from the absorption site. Mucoadhesive polymers can be used to prevent rapid clearance of the drug formulation, increasing nasal residence time and thereby allowing longer absorption times. To enhance nasal absorption of large molecular weight and polar molecules, absorption enhancers have been widely employed. However, absorption of such polar molecules across the nasal mucosa can also be greatly increased by the use of polymers able to transiently open the tight junctions between the epithelial cells.

Among different polymers, chitosan, the *N*-deacetylated product of the polysaccharide chitin, is gaining increasing importance in medical and pharmaceutical applications due to its good mucoadhesion and absorption-enhancing ability. Moreover, chitosan shows the ability to form hydrogels that are able to control the rate of drug release from the delivery system as well as protect the drug from chemical and enzymatic degradation at the administration site. In particular, when chitosan is chemically or physically cross linked, a three-dimensional network is formed in which the drug can be incorporated to control its release.

Recently, we prepared small cone-shaped inserts based on chitosan polyelectrolyte complexes with the aim of delivering a unique dose of drug in the nasal cavity and achieving a controlled release of the active principle according to hydration/diffusion mechanisms. Nasal inserts prepared with chitosan/pectin (2) or chitosan/hyaluronic acid (3) complexes were obtained by lyophilisation with or without model drugs such as vancomycin, insulin, and chlorpromazine. Complexation yield along with thermal analysis were preformed to study the degree of interactive strength between polyions. Morphological characteristics, water uptake, mucoadhesion, drug release, and permeation tests were performed to investigate the ability of the insert to deliver the loaded drug in the nasal cavity.

The interaction of polycation with polyanion during the preparation of polyelectrolyte complexes leads to physically cross-linked hydrogels (4,5), which can retain a great amount of water at the interior. As nasal inserts were obtained by lyophilisation, which consists of sublimation of the frozen water yielding to the formation of pores or channels in the polymer, all the samples were characterized by a sponge-like structure (Figure 1).

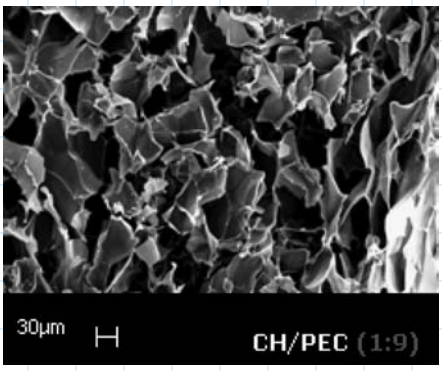

Figure 1. *Characteristic sponge-like structure of a lyophilised insert based on chitosan complexes.*

Figure 2 show the effect of chitosan/polyanion (A, CH/PEC; B, CH/HA) molar ratio on complex formation at various pH levels. Since the pK_a value of chitosan was 6.3, in the 2.0 to 5.0 pH range the theoretical percent ionization of chitosan ($-NH_3^+$) was about 100%. In contrast, the percent ionization of hyaluronic acid (pK_a 2.9) and pectin (pK_a 4.0) decreased with decreasing pH levels in the media. At pH 2.0, 3.0, 3.5, 4.0, and 5.0 the theoretical percent ionization of

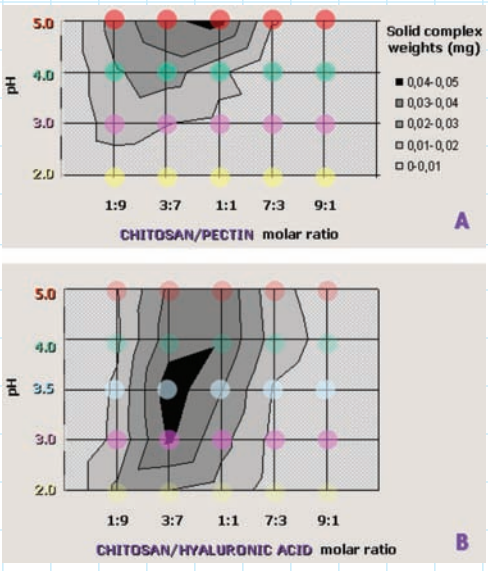

Figure 2. *Effect of chitosan/polyanion (**A**, CH/PEC; **B**, CH/HA) molar ratio on complex formation at various pH levels.*

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pectin (–COO⁻) was 1, 9, 24, 50, and 91%, respectively, while the theoretical percent ionization of hyaluronic acid (–COO⁻) was 11, 56, 80, 93, and 99%, respectively. This suggests that much larger amounts of pectin and hyaluronic acid molecules were required to interact with chitosan molecules at low pH levels.

The water uptake, mucoadhesion, drug release, and permeation ability of the different complexes can be modulated by adequate selection of preparative condition. In particular, we found that conditions favouring a low degree of interaction in the complex between chitosan and polyanion molecules and the presence of a large amount of free negative or positive charges could enhance water uptake ability and mucoadhesiveness and allow good control of drug release at the absorption site followed by sustained permeation profiles (Figure 3).

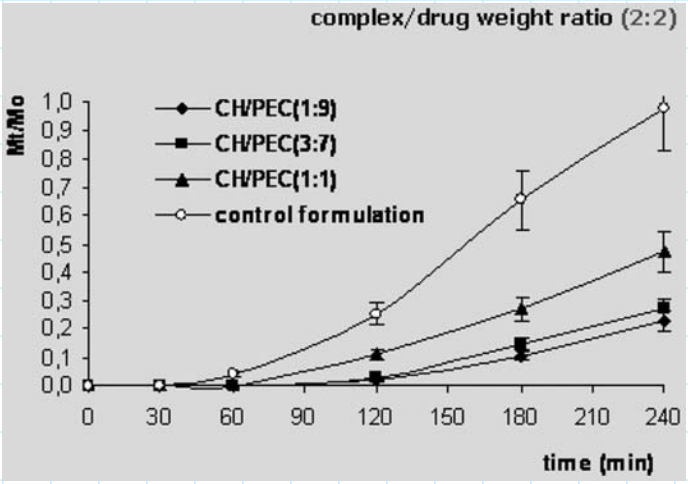


Figure 3. *Permeation profiles relative to nasal inserts based on CH/PEC complexes.*

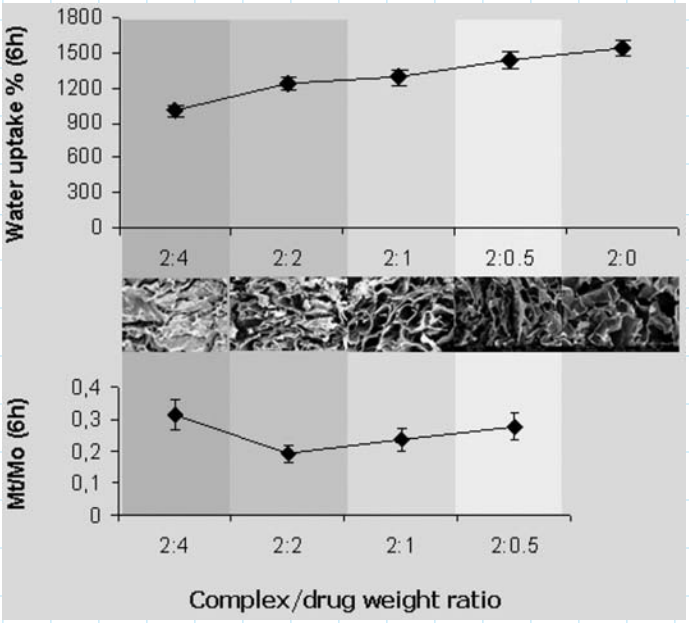


Figure 4. *Drug release versus water uptake for the nasal insert based on CH/PEC (1:9) ratio.*

We also observed that drug–complex interactions could influence the final behaviour of nasal inserts. For example, inserts based on chitosan/pectin complex obtained at pH 5.0 with an excess of pectin (1:9 CH/PEC molar ratio) could interact with the drug chlorpromazine hydrochloride (pK_a 9.3) by means of ionic bonds between the negatively charged pectin and the positively charged drug. The presence of complex–drug interactions resulted in less porous inserts, lower water uptake ability, and, thus, lower drug availability at the absorption site (Figure 4).

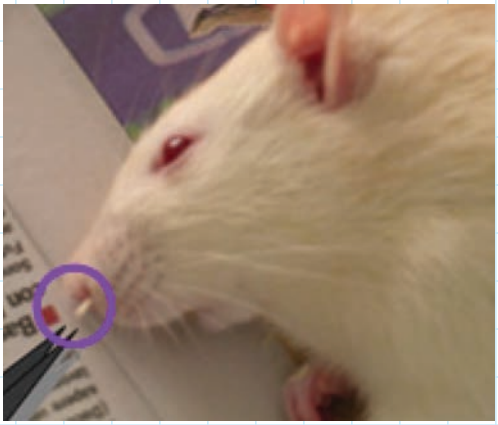


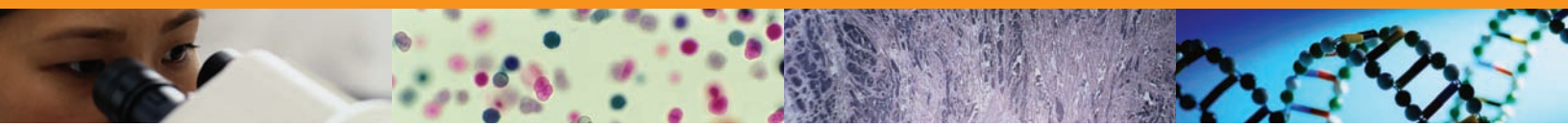
Figure 5. *Small nasal inserts administered in the nasal cavity of rats.*

Finally, small nasal inserts (1 mm diameter) were prepared with CH/PEC and CH/HA complexes and were administered in the nasal cavity of rats (Figure 5). The results showed no irritation of the mucosa during the period of administration (4 hr).

Chitosan polyelectrolyte complexes can be employed for the formulation of mucoadhesive nasal inserts with different drug-release properties. The selection of a suitable pH and chitosan/polyanion molar ratio during complex preparation allowed the modulation of insert behaviour at the administration site. This work has contributed to the understanding of chitosan-based polyelectrolyte complex formation and will be furthered by performing intranasal absorption studies in animal models.

References

1. Illum, L. Nasal drug delivery: Possibilities, problems and solutions, J. Control. Release 87: 187-198 (2003).
2. Bigucci, F, Luppi, B, Cerchiara, T, Sorrenti, M, Bettinetti, G, Rodriguez, L, Zecchi, V. Chitosan/pectin polyelectrolyte complexes: Selection of suitable preparative conditions for colon-specific delivery of vancomycin, Eur. J. Pharm. Sci. 35(5): 435-441 (2008).
3. Luppi, B, Bigucci, F, Mercolini, L, Musenga, A, Sorrenti, M, Catenacci, L, Zecchi, V. Novel mucoadhesive nasal inserts based on chitosan/hyaluronate polyelectrolyte complexes for peptide and protein delivery, J. Pharm. Pharmacol. 61(2): 151-157 (2009).
4. Berger, J, Reist, M, Mayer, JM, Felt, O, Peppas, NA, Gurny, R. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications, Eur. J. Pharm. Biopharm. 57: 35-52 (2004).
5. Luppi, B, Bigucci, F, Cerchiara, T, Zecchi, V. Chitosan-based hydrogels for nasal drug delivery: From inserts to nanoparticles, Expert Opin. Drug Deliv. 7(7): 811-828 (2010). ■



Research and Development Resources: TNO Science and Industry

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

TNO Science and Industry, a non-profit contract research organization in the Netherlands, has provided research and development services to support innovation in a broad range of industries for many years. Controlled release technologies have become a focal area of the organization. A series of questions were presented to Dr. Nicole Papen-Botterhuis, a researcher in the Innovative Materials Department at TNO, to probe both the overall scope of TNO and areas of controlled release embodied there. Her answers provide a glimpse of the history, makeup, and approach to controlled release technical developments of TNO.

Q ***What Is TNO?***

A TNO is an independent non-profit research organization with approximately 4,500 employees in the Netherlands. Our mission is to apply scientific knowledge with the aim of strengthening the innovative power of industry and government. Sometimes we develop knowledge ourselves, but in other cases we can apply the knowledge developed by universities to solve our customers' problems.

What I like about TNO is that you can find scientists from all disciplines within our organization, from chemistry to mechanical engineering, from psychology to physics. Together you can find innovative solutions and new application areas for existing technology.

Figure 1. *Different stages of projects within TNO.*

Q ***Why Was TNO Started?***

A TNO was founded as the result of a law that came into force in 1930 in the Netherlands, stating that there should be an institute in the Netherlands for the application of scientific knowledge to solve problems in industry, agriculture, and society. Although we exist by law, TNO is not a governmental organization and is independent of public and private interest.

Q ***Where and When Did TNO Originate and Where Does It Reside Today?***

A TNO started in a small office in The Hague, but soon many governmental research labs were taken over and new departments were founded all over the Netherlands. Currently, we have labs and offices in Delft, The Hague, Utrecht, Eindhoven, Leiden, Zeist, Soesterberg, Rijswijk, Helmond, Enschede, Groningen, and Den Helder, usually close to universities or in science parks.

Figure 2. *Twelve locations of TNO in the Netherlands.*

Q ***Has the Charter of TNO Changed Since Its Beginnings?***

A Over the years, TNO has become more market-oriented. This is partly due to a reduction in governmental funding, but also due to a change in the "TNO-law" in 1985, stating that TNO has to deliver a strategic plan every four years, defining the research programs in accordance with stakeholders and government.

Q ***How Is TNO Organized?***

A From the first of January, 2011, TNO will have a new structure in which we will focus our work into seven themes: Healthy Living; Industrial Innovation; Mobility; Energy; Built Environment; Information Society; Safety, Security and Defense. New projects have to contribute to solving the societal or industrial problems that are defined in these themes.

Q ***What Areas of TNO Are Involved with Controlled Release Technology?***

A Many! We have people from chemistry, materials technology, and biochemistry who are working on new materials and formulations for controlled release systems, people from

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toxicology and pharmacology who are working on the TNO intestinal model (TIM) for a correct predication of dissolution and uptake of pharmaceutical formulations via the gastrointestinal tract, and people from mechatronics who are building new encapsulation equipment.

Q ***What Has Historically Made Up the Client Base of TNO as a Whole and/or in Controlled Release Research?***

A The client base of TNO as a whole is too broad to discuss here, but it ranges from startups to SMEs to multinationals. In controlled release, our client base [consists] mainly of companies active in food, construction materials, coatings, pharma, personal care, and homecare. Many of these companies are Dutch or have a local research centre or sales office here; however, we do see a shift as TNO is receiving more attention internationally.

Q ***How Do Projects Initiate in TNO?***

A There are many different ways. We have consultancy projects, in which TNO advises customers based on knowledge gained over the years in many different areas. Furthermore, if we discover an unmet need in a certain market and we want to develop an interesting technology to fulfill this need, we can do this by ourselves, in EU programs using governmental funding or in collaboration with companies with partial governmental funding. As soon as the knowledge development phase is finished, we can no longer use governmental funding, and bilateral projects with companies are initiated. After a feasibility study, companies can have a license on our patents. In some cases our business developers come across a customer problem that can be solved by using a technology that was developed by TNO in a different area. This is one of the major advantages of TNO and also explains why it is so important that all people within TNO are connected and aware of the developments in other departments. This knowledge sharing is supported in several ways, including ICT systems and internal conferences and presentations.

Q ***Do the Policies and Practices within TNO Foster Inter-department Interactions and Collaboration?***

A Yes, we have many projects in collaboration with other departments within TNO. Some departments, like mine (Innovative Materials), develop enabling technologies and knowledge that can be used in different applications for different markets. Other departments work for one specific market, like "oil and gas" or "defense." These departments are always looking for technologies that can solve problems in their market. Sometimes they find the solution in our department or at least we can help them to find the right solution. For example, we cooperate with our colleagues from the Built Environment Department in the European project Axioma for the development of controlled release systems in building materials. In another European project, Prospie, we develop an encapsulation method for our colleagues from the Defense and Security Department who are developing safe personal protection equipment for workers in industrial environments.

Q ***Are There Any Unique Controlled Release Research or Technologies Directly or Indirectly Linked to TNO Efforts that You Can Share?***

A In the field of controlled release, TNO has several activities. TNO has developed the BioSwitch system, in which a cross-linked biopolymer matrix is used to encapsulate active ingredients. TNO was honored by *Scientific American* with a place in its top 50 in 2007 for the development of this system. The BioSwitch concept represents the enzymatically triggered release of an active compound from a cross-linked biopolymer microcapsule. The biopolymer cage retains the active by multi-ionic interactions until enzymes degrade the polymeric structure (1,2). BioSwitch capsules can be used as a release-on-command additive in wet and dry formulations. Depending on the enzymatic action present in the application, a tailored biopolymer matrix can be proposed. Post-treatment of the capsules (secondary encapsulation, heat treatment, etc.) can further enhance the efficacy under specific environmental conditions.

Secondly, TNO has developed the TNO Intestinal Model (TIM), which simulates all the different parts of the gastrointestinal tract by imitating the chemical and physical conditions. This *in vitro* system is used by many pharmaceutical companies to test the (site-specific) release and dissolution of their drug formulations (e.g., under fed and fasting state conditions or simulated disease conditions) and gives a realistic value for the amount of drug that is available for uptake through the intestinal wall (3).

Further, TNO has developed many controlled release systems based on mineral particles such as clay. Clay has an extremely high capacity to bind components. This can be used to slow down the release of these components from a matrix. We were also able to tune the dissolution rate of different clay types, thereby controlling the release rate of the components that are bound to the clay.

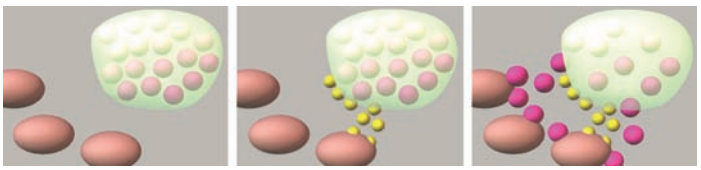

Figure 3. *Example of triggered release from BioSwitch particles. Bacteria produce enzymes (yellow particles) that can degrade the BioSwitch particle, thereby releasing antibacterial agents (pink) that kill the bacteria. If no more enzymes are produced/present, the release of antibacterial agents stops.*

Q ***Does TNO See Any Unique Areas Where It Has a Significant Potential to Contribute Now or in the Future?***

A This is definitely the encapsulation printer, which is a result [of] the collaboration between the mechatronic engineers and material scientists. With this equipment, we can encapsulate monodisperse liquid droplets by shooting them through a liquid film of shell material. It is a completely new method of making capsules, and at the CRS meeting in Portland, I had many positive reactions on my presentation about this technique. We can either encapsulate an aqueous solution with a fatty shell or an oily substance with a polymer shell, for instance spherical oil capsules with a diameter of 280 µm and a carrageenan shell of 7 µm. We are now actively looking for more components that cannot be encapsulated in certain shells with the conventional methods. So, if any of the readers has an interesting suggestion, we can always try to make suitable encapsulations and perhaps even test them in the TIM on protecting and releasing features!

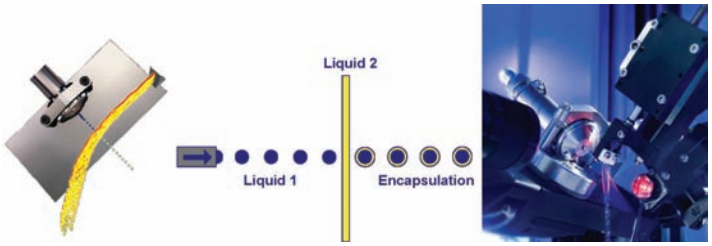

Figure 4. *Working principle of the encapsulation printer and stroboscopic picture of the encapsulation printer in action.*

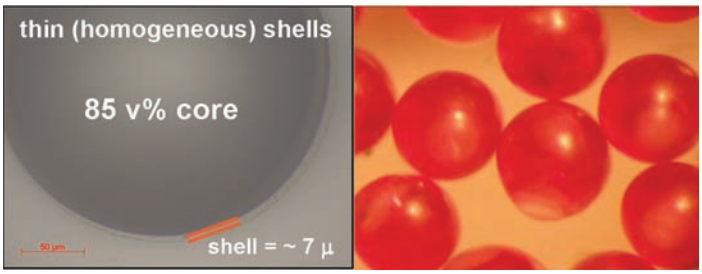

Figure 5. *Two examples of particles produced with the encapsulation printer. Left: oil with a carrageenan shell. Right: syrup particles (approx. 250 µm) with a fatty shell.*

Q ***Is There Any Other Information or Thoughts on TNO that You Would Like to Share?***

A I hope the readers have enjoyed my story and share at least some of my enthusiasm about TNO. If they have further questions, they can contact me via e-mail: nicole.papen@tno.nl.

References

1. de Jong, AR, et al. Food Addit. Contam. 22(10): 975-979 (2005).
2. Slaghek, T. Chem. Ind. 4: 24-25 (2008).
3. Tenjarla, S, et al. Adv. Ther. 24(4): 826-840 (2007). ■

14th Industrial Symposium and 5th Trade Fair on Microencapsulation

The 14th Industrial Symposium and 5th Trade Fair on Microencapsulation will be held March 7–9, 2011, at the Sheraton Gunter Hotel in San Antonio, TX, and is being organized by the Bioencapsulation Research Group and Controlled Release Society. This will be an excellent opportunity to get up-to-date information regarding microencapsulation; meet industrial leaders; find new partners, suppliers of R&D services, products, materials, equipment; and license or advertise your new technologies. The three-day event will offer lectures from leading experts, exhibitors from state-of-the-art microencapsulation companies, scheduled one-on-one meetings with fellow attendees, and process demonstrations at the Southwest Research Institute. Additional information and registration details are available online at http://impascience.eu/bioencapsulation/2011_San_Antonio/.

Riverwalk in San Antonio/Kenny Braun

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Cyclodextrins in Injectable Drug Delivery of Poorly Soluble Compounds

Zimei Wu,[1] Ian G. Tucker,[2] Majid Razzak,[3] Keith McSporran,[4] and Natalie J. Medlicott[2]

Introduction

Post-injection drug precipitation is one of the concerns associated with parenteral drug delivery for poorly water soluble drugs in both human and veterinary formulation development. It can cause problems in several ways: 1) mechanical irritation; 2) irritation to the tissues at the injection site due to prolonged drug-tissue contact time; and 3) the likelihood of poor and less reproducible systemic bioavailability. In the agricultural setting, these injectable formulations are unacceptable both from the perspective of animal welfare and carcass spoilage in the case of livestock. Carcasses with aesthetic tissue damage and drug residues adversely impact the economy, and the cost of trimming prior to marketing is high. It has been reported that injection lesions and scars cause an estimated average loss of $19 million annually in the Canadian beef industry (1).

Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. CDs have been widely used to enhance drug absorption by increasing drug solubility and dissolution rate. In addition, through formation of inclusion complexes with lipophilic drugs CDs can mask certain physicochemical characteristics of the included molecule such as irritation after injection, taste, and incompatibility of drugs and excipients. For parenteral formulations, prevention of precipitation of poorly soluble drugs due to solubility enhancement is also well reported.

Ricobendozole (RBZ) is a poorly water-soluble benzimidazole anthelmitic used in veterinary medicine. The commercial product, formulated with co-solvency at low pH, is reported to have a bioavailability of 40% and to cause injection site reactions after subcutaneous (sc) injection in calves (2). The authors suggested that these problems were both attributable to post-injection drug precipitation. This article reports an investigation on the effect of hydroxypropyl-β-cyclodextrin (HP-β-CD; 20%, wt/vol) on the tissue compatibility and pharmacokinetics of a 5% low pH RBZ formulation (pH ≈1.5). The mechanisms by which HP-β-CD improved RBZ absorption are discussed.

***In Vitro* Studies**

Preformulation studies showed that complexation of RBZ with HP-β-CD was low. The solubility in 20% HP-β-CD solution was only 1.6 mg/mL. Sufficient solubility for a formulation (50 mg/mL) could not be achieved unless low pH (<1.5) was combined. Further studies showed that addition of HP-β-CD stabilized the low pH RBZ solution against precipitation upon dilution/neutralization with buffer (pH 7.4), simulating the *in vivo* situation. The HP-β-CD formulation remained clear for longer than a comparably diluted acidic solubilized solution (Figure 1). This suggested HP-β-CD could stabilize a supersaturated RBZ solution. This stabilizing effect was found to

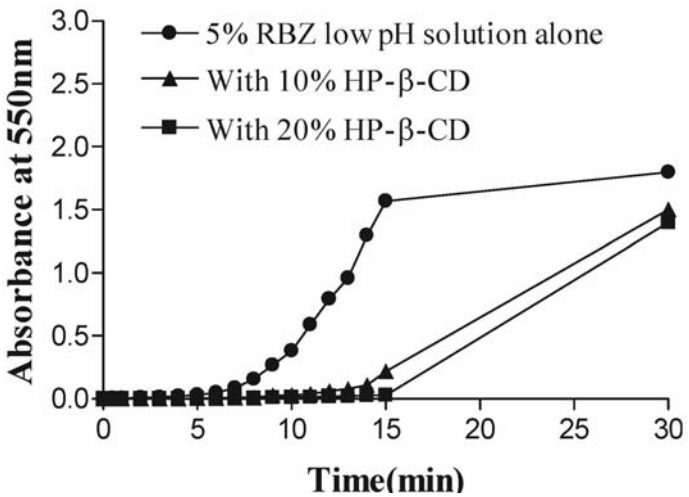

Figure 1. *Effects of HP-β-CD on precipitation of RBZ from 1 mL of solution (pH = 1.5) upon dilution with 2 mL of phosphate buffer (0.1*M*, pH 7.4) monitored by measurement of light scattering at 550 nm.*

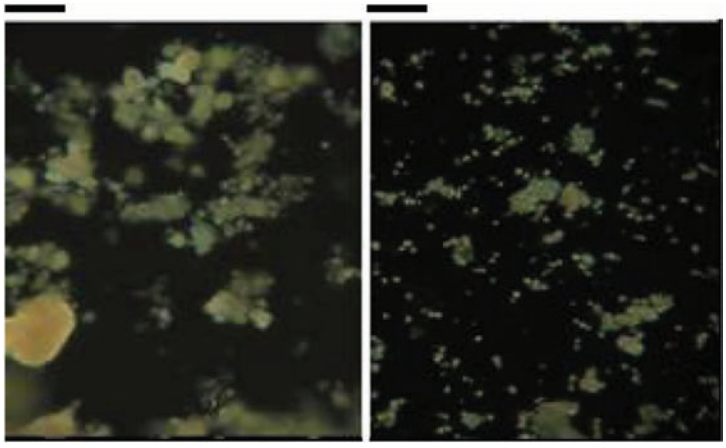

Figure 2. *Microscopic appearance of RBZ precipitate after neutralisation by phosphate buffer (0.1*M*, pH 7.4) in the absence (left) and presence (right) of 20% (wt/vol) HP-β-CD. Bars above the figure indicate 50 µm.*

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[2] School of Pharmacy, University of Otago, Dunedin, New Zealand.
[3] PharmTech Service Ltd., Auckland, New Zealand.
[4] Gribbles Veterinary, Auckland, New Zealand.

From the Vet Group continued on page 22

From the Vet Group continued from page 21

be more effective than the commonly used pharmaceutical solvents (3). Microscopic observation suggested that in the presence of HP-β-CD the resultant precipitate (<10 μm) had a smaller particle size (Figure 2).

Tissue Tolerance and Pharmacokinetics in Sheep

Tissue tolerance and pharmacokinetics were simultaneously investigated after sc injection in sheep. Benzyl alcohol (BA, 0.9%, wt/vol) was added to both formulations as a local anaesthetic. Sheep were divided into two groups: low pH formulation group (n = 5) and HP-β-CD formulation group (n = 6). Each animal received a formulation on one side of the back at a dose of 0.1 mL/kg (equivalent to RBZ at 5 mg/kg) and the respective vehicle of the same volume on the contralateral side. Injection site reaction was evaluated by observation of 1) signs of pain on injection; 2) swelling and redness at the injection site; 3) elevation in plasma creatine kinase (CK) concentration; and 4) tissue histology at the injection site at 7 days.

The 20% HP-β-CD solution without RBZ showed good tissue tolerance in sheep after sc injection, with no evidence of injection site reactions or histological changes in the tissue. Injection of the HCl solution containing BA caused minimal pain and swelling in one of the animals. RBZ formulations at low pH, with and without HP-β-CD, resulted in pain on injection and swelling in two animals in each group. Interestingly, addition of benzyl alcohol reduced pain more effectively for the low pH formulation than for the HP-β-CD formulation, possibly due to the complexation of BA into HP-β-CD that resulted in a loss of anaesthetic effect. Tissue histology at 1 week suggested that minimal to mild necrosis occurred in the tissues in some sheep in both groups. However, minimal necrosis at an early stage of tissue damage may recover in time through tissue regeneration (4). Lack of elevation of CK, even when the respective vehicle was injected simultaneously, indicates that both formulations caused no significant damage to the underlying muscles in sheep. Tissue samples taken at 2 weeks in a separate study showed tissue granulation in low pH formulation-treated animal, whereas no significant change was observed in HP-β-CD formulation-treated animal.

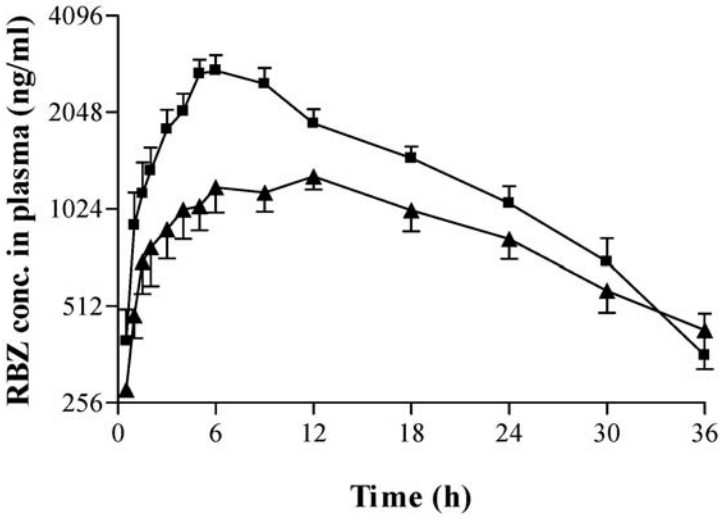

Figure 3. *Mean plasma concentration–time profiles of RBZ after sc administration in sheep of the low pH formulation (triangles,* n = *5) and the HP-β-CD formulation (squares,* n = *6) at a dose of 5 mg/kg. Data are means ± SE.*

The C_{max} and t_{max} for the low pH formulation were 1.3 ± 0.3 μg/mL and 9.6 ± 2.9 hr, respectively, while the corresponding data for HP-β-CD formulation were 2.9 ± 0.8 μg/mL and 5.0 ± 0.6 hr, respectively (Figure 3). Compared with the reference formulation, the $AUC_{0-\infty}$ for the HP-β-CD formulation was 1.6 times higher. This was similar to that for intravenous administration in sheep at the same dose (5), suggesting that RBZ absorption from the HP-β-CD formulation might be virtually complete.

The Roles of HP-β-CD in RBZ Absorption

The absorption enhancement by HP-β-CD of RBZ is postulated to be mainly due to 1) HP-β-CD inhibition of post-injection drug precipitation through stabilization of the supersaturated solution created as tissue fluids dilute the formulation at the injection site. Together with a small direct solubilizing effect, this would lead to a longer time for drug absorption from a higher concentration level. 2) HP-β-CD may act as a permeability enhancer by carrying the drug through the aqueous barrier, from the bulk solution toward the surface of the biological membrane. 3) The reduction in the size of precipitate (<10 μm) ensures rapid re-dissolution and causes less irritation.

Conclusions

HP-β-CD was shown to be a tissue-compatible excipient with potential to inhibit post-injection precipitation and increase absorption of the poorly water-soluble drug RBZ without causing more irritation than the solution formulation. Since bioavailability is improved, a smaller dose may be equally effective, and a formulation with lower drug concentration may further improve tissue compatibility.

Acknowledgments

Financial support was provided by the Foundation for Research, Science and Technology New Zealand and Bomac Laboratories Ltd., Auckland.

References

1. Van Donkersgoed, J, Dixon, S, Brand, G, VanderKop, M. A survey of injection site lesions in fed cattle in Canada, Can. Vet. J. 38: 767-772 (1997).
2. Formentini, E, Mestorino, O, Marino, E, Errecalde, J. Pharmacokinetics of ricobendazole in calves, J. Vet. Pharm. Therap. 24: 199-202 (2001).
3. Wu, Z, Tucker, IG, Razzak, M, Medlicott, NJ. An *in vitro* kinetic method for detection of precipitation of poorly soluble drugs, Int. J. Pharm. 304: 1-3 (2005).
4. Chandrasoma, P, Taylor, CR. Concise Pathology, Appleton & Lange, Norwalk, CT, pp1-50 (1991).
5. Goudah, A. Aspects of the pharmacokinetics of albendazole sulphoxide in sheep, Vet. Res. Commun. 27: 555-566 (2003). ■

Israeli Chapter of CRS (ICRS) Holds 7th Annual Meeting

Prof. Rosa Azhari
ORT Braude College, Karmiel, Israel

The 7th Meeting of the Israeli Chapter of the Controlled Release Society (ICRS) took place in Haifa, Israel, October 3–4, with 170 members of ICRS from industry and academia participating in the meeting. The meeting focused on new trends in drug delivery and controlled release-based products. The program consisted of four keynote lectures, invited talks, short oral student presentations, and poster presentations.

The first keynote speaker was Prof. Henry Kopecek (University of Utah), who reviewed the use of polymeric drug carriers, discussed recent advances in the development of new copolymer-drug conjugates, and presented a new paradigm in drug delivery based on the biorecognition of peptides on cell surfaces, which leads to control of apoptosis of cells. The first session on "Novel Anti-cancer Therapies" was opened by Prof. Alberto Gabizon, who reviewed the development of Doxil from bench to bedside and described new PEGylated liposomal prodrug formulations for treatment of cancer. Dr. Ronit Satchi-Fainaro described the design of multifunctional therapeutics, combining targeting moieties and anti-tumor and anti-angiogenic drugs, for cancer theranostics, and Dr. Ayelet David discussed novel polymer conjugates, combining cell penetrating peptides and activated by light, for cancer detection and therapy. Dr. David Stepansky reported the use of ER-targeting peptides for intracellularly targeted drug delivery.

From left to right: Profs. Smadar Cohen (winner of the 2010 ICRS Prize for Outstanding Achievements in Controlled Release), Chezy Barenholz, and Rosa Azhari (former president of ICRS), and graduate student Emil Rubinov.

In a keynote lecture Prof. Paolo Caliceti (University of Padova, Italy) discussed supramolecular bioconjugates for drug delivery, focusing on systems combining gold nanoparticles with targeting moieties and polymers conferring stimuli-sensitive (pH or temperature) properties to the colloidal systems. The second session, "Imaging, Diagnostics and Product Characterization in Advanced Drug Therapies," included presentations by Dr. Galia Blum on non-invasive cancer imaging using near infrared fluorescent cathepsin activity-based probes, Prof. Yeshayahu Talmon on advanced cryo-electron microscopy in the study of nano-aggregates in liquid and semi-liquid systems, and Dr. Elena Khazanov on immunosensing platforms for optical detection of cancer biomarkers in the lumen of the GI tract.

A session on "Bioavailability and Oral Delivery" concluded the first day of the meeting. In this session Prof. Simon Benita (head of the school of Pharmacy, Hebrew University of Jerusalem) described a novel oral formulation that markedly enhances docetaxel absorption via the lymphatic route. In this formulation, nanocapsules of docetaxel are embedded in entero-coated, bioadhesive microparticles that enable bypass of the gut barriers for docetaxel absorption. Prof. Amnon Hoffman described the development of gastro-retentive formulations for various types of drugs and the use of backbone cyclization to convert active peptides into metabolically stable entities. Prof. Eyal Shimoni reported the use of amylose complexes to enhance the bioavailability of edible bioactives, and Dr. Sigal Saphier demonstrated a method for tracking enterically coated capsules in the gastrointestinal tract using X-ray imaging.

The second day of the meeting was opened with a keynote lecture by Prof. Alexander Levitzki, who described the use of non-viral "Trojan horses" bearing targeting moieties, mainly EGF, to direct double-stranded RNA (dsRNA) to cancer cells. The dsRNA evokes signal transduction pathways that activate specific immune responses leading to the death of tumor cells.

Members of the Organizing Committee and keynote speakers. From left to right: Profs. Avri Rubinstein, Smadar Cohen, Paolo Caliceti, and Rosa Azhari, Dr. Ronit Satchi-Fainaro (elected president of ICRS), Profs. Rimona Margalit and Henry Kopecek, and Dr. Ayelet David.

Gala Dinner at the Pine Club. From left to right: student Yosi Shamay, Dr. Ayelet David, Keynote Speakers Profs. Henry Kopecek and Paolo Caliceti, Dr. Elena Khazanov, and Prof. Avri Rubinstein.

In the session on "Issues in Inflammation and Immunomodulation," Prof. Gershon Golomb talked about immunomodulation by nanoparticles in cardiovascular disorders, Dr. Dan Peer discussed the challenges and opportunities of RNAi nanomedicine, Dr. Yaron Dekel described novel fibrillar insulin formulations for oral administration, and Efrat Harel described the use of PEGylated nano-immunoliposomes targeting transferring receptors for local treatment of inflammatory bowel diseases via the luminal route.

The next session was devoted to the commercialization of drug delivery products and opened with an exciting keynote talk by Dr. Avi Molcho (a venture partner at Forbion Capital Partners and an experienced entrepreneur), who discussed the life cycle of a startup from an entrepreneur's perspective and an investor's point of view. The participants heard a presentation on patent protection for innovations in controlled release drug technologies, given by Dr. Keren Hagain (Eyal Bressler & Co. Patent Attorneys). Dr. Galit Levin described the recent results of TransPharma Medical's RF transdermal technology for treating osteoporosis and diabetes in a talk titled "Eliminating Needles: Therapeutic Delivery of Peptides and Oligonucleotides Through Skin." Prof. Fuad Fares concluded this session and talked about the development of ModigeneTech technology for designing long-acting proteins by attaching, recombinantly, oligosaccharides to the proteins.

The last session of this meeting addressed controlled release in tissue regeneration technologies. Prof. Shulamit Levenberg described local stimulations in 3D for controlled differentiation and organization of embryonic stem cells, Prof. Meital Zilberman described the use of antibiotic-eluting composite structures for wound-healing applications, Dr. Sarit Sivan talked about a novel solvent/non-solvent technique for producing sequential, multi-component–releasing scaffolds for tissue engineering, Dr. Liat Oss-Ronen described novel hydrogels used as scaffolds designed with affinity-based drug delivery, Emil Rubinov showed that sequential delivery of IGF-1 and HGF from injectable alginate promotes myocardial repair after myocardial infarction, and Yael Lupu concluded the meeting by describing bioactive ceramic scaffold-conjugated PLGA particles for bone tissue engineering.

From the 48 poster presentations, 11 students were chosen to give 5-minute presentations during the podium sessions. All the students participated in the best student presentations competition. More details on the presentations can be found in the abstract book published on the ICRS website at www.icrs.org.il (meeting 2010).

One of the traditional events of the ICRS meetings is the Gala Dinner. This year the Gala Dinner took place at The Pine Club in the Carmel forests. Good food, wine, and beer led to informal meetings between participants. The highlight of the dinner was the presentation of the ICRS prizes.

Prof. Smadar Cohen was awarded the ICRS Prize for Outstanding Achievements in Controlled Release, in recognition of her contribution to the field of controlled release in tissue regeneration technologies.

Plaques were presented to the winners of the 2009 Student Presentation Competition: First Prize (travel grant and registration to a CRS meeting) was awarded to Daniel Zucker (supervisor Prof. Yechezkel Barenholz), Department of Biochemistry, Hebrew University-Hadassah Medical School, Jerusalem) for his presentation on "Cancer Therapeutic Efficacy of Two Drug Combinations Co-remote Loaded into Nanoliposomes: Relevance of *in Vitro* Synergy." Second Prize (travel grant to a CRS meeting) was awarded to Ehud Segal (supervisor Dr. Ronit Satchi-Fainaro), Department of Physiology and Pharmacology, Sackler School of Medicine, Tel Aviv University, for his presentation on "RAFT-Synthesized Nanoconjugates for Targeting Bone Metastases and Calcified Neoplasms." Ehud presented a podium talk and also served as co-chair of a session at the 37th CRS Annual Meeting in Portland, OR. Third Prize (1,000 IS each) was awarded to Eva Kopansky (supervisor Dr. Ayelet David), Department of Pharmacology, Faculty of Health Sciences, Ben-Gurion University, for her presentation on "Polymer Conjugates for Visualizing Solid Tumors in the GI Tract," Lior Raviv (supervisor Dr. Ayelet David), Department of Pharmacology, Faculty of Health Sciences, Ben-Gurion University, for his presentation on "Mannosylated Block Copolymer Micelles for Targeting Genes into Antigen-presenting Cells," and Emil Rubinov (supervisor Prof. Smadar Cohen), Department of Biotechnology Engineering, Faculty of Engineering Sciences, Ben-Gurion University, for his presentation on "Affinity-binding Alginate Biomaterial for the Controlled Delivery of Cardiovascular-Protective Factors."

The winners of the 2010 Student Presentation Competition were announced at the Gala Dinner. The 2010 student prizes was sponsored by Prof. Chezy Barenholz. First Prize (travel grant and registration fee to a CRS meeting) was awarded to Ekaterina

Chapter News Israeli continued on page 26

Chapter News Israeli continued from page 25

Perets (supervisor Prof. Joseph Kost), Department of Chemical Engineering, Ben-Gurion University, for her presentation on a "Controlled Delivery System to Elicit Anti-cancer Effects of HIV Protease Inhibitor Nelfinavir." Second Prize (travel grant to a CRS meeting) was awarded to Paula Ofek (supervisor Dr. Ronit Satch-Fainaro), Department of Physiology and Pharmacology, Sackler School of Medicine, Tel-Aviv University, for her presentation on "*In Vivo* Delivery of siRNA to Tumors and Their Vasculature by Novel Dendritic Nanocarriers." Third Prize (1,000 IS each) was awarded to Anna Elgart (supervisor Prof. Amnon Hoffman), Institute for Drug Research, School of Pharmacy, Hebrew University of Jerusalem, for her presentation on "Self Nano-emulsifying Drug Delivery Systems (SNEDDS) for Improved Bioavailability of BCS Class 2 Compounds: Effects on Solubilization, Intra-enterocyte Metabolism and P-gp Efflux"; Efrat Harel (supervisors Prof. Avri Rubinstein and Dr. Boaz Tirosh), Institute of Drug Research, School of Pharmacy, Hebrew University of Jerusalem, for her presentation on "Transferrin Receptor as a Potential Target Molecule for the Local Treatment of Inflammatory Bowel Diseases via the Luminal Route"; Shoshy Mizrahi (supervisor Dr. Dan Peer), Laboratory of Nanomedicine, Department of Cell Research and Immunology, Tel Aviv University, for her presentation on "Hyaluronan Coated Nanoparticles: Does Size Matter?"; and Yosi Shamay (supervisor Dr. Ayelet David), Department of Clinical Pharmacology, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, for his presentation on "E-Selectin Targeted Polymer Conjugates for Treatment of Primary Tumors and Lung Metastases."

Participants enjoy good food and conversation at the Gala Dinner.

We are indebted to our sponsors: the Controlled Release Society, Teva Pharmaceutical Industries, Dexcel Pharma, Taro Pharmaceutical Industries, The Russel Berrie Nanotechnology Institute at the Technion, The David R. Bloom Center of Pharmacy at the Hebrew University of Jerusalem, ORT Braude College, and Trans Pharma Medical. The continuing support of our sponsors enables the participation of students at a low cost and provides the seed funds for the activities of ICRS.

During ICRS7 the members of ICRS elected a new Executive Committee: Dr. Ronit Satchi-Fainaro was elected as president of ICRS, Dr. Ayelet David as treasurer, Profs. Rimona Margalit and Noah Lotan as members of the Audit Committee, and the following members of the Board: Dr. Sigal Blau, Prof. Marcelle Machluf, Dr. Adel Penhasi, Prof. Avri Rubistein, and Dr. Boaz Tirosh. In addition to the elected members, the two former presidents of ICRS, Profs. Rosa Azhari and Elka Touitou, also serve as Executive Committee members. ■

Stress and Strain Can Make You Thin (Unless You're Made of Custard)

UKICRS at the British Science Festival, September 14–19, 2010

Daniel Kirby, Sarah McNeil, Behfar Moghaddam, Jitinder Wilkhu, and Yvonne Perrie

The British Science Festival, one of Europe's largest celebrations of science, engineering, and technology, takes place annually in September. Each year the festival travels to a different U.K. location and this year the festival was held in Birmingham, with many events taking place within the Aston University Campus. The festival connected a huge range of people with scientists, engineers, technologists, and social scientists through celebrity appearances, topical debates, and fascinating hands-on fun. The aim of the festival is to celebrate the sheer excitement of the latest developments and also to engage in open discussion about issues that interest and concern large numbers of people about scientific advancement. The festival hosted more than 250 events, and as part of this, the Aston Pharmacy School in conjunction with UKICRS ran an interactive family exhibit titled "Stress and Strain Can Make You Thin, Unless You're Made of Custard."

As you might guess from the title, one of our stalls focused on non-Newtonian fluid properties and, in particular, custard. But not just any custard—this was Birmingham's custard. Indeed, there is more association between Birmingham, pharmacy, and custard than you might first realise. Alfred Bird registered as a pharmacist in Birmingham in 1842, and went on to open an experimental chemist's shop in Bull Street. His wife was a big fan of custard, but unfortunately, due to her being allergic to eggs and yeast she was unable to enjoy it. Thanks to his formulation

The team starts making 40 L of custard and then gets distracted by playing with it.

training, Alfred Bird invented a corn flour-based, egg-free custard in 1837, which became known as Bird's custard. Alfred Bird also went on to invent baking powder and blancmange. The custard factory in Digbeth, Birmingham—originally built by Sir Alfred Frederick, the son of Alfred Bird—is where production of Bird's custard took place until 1964. This old factory still stands and was redeveloped in 1992 but now houses artists and other small businesses.

An active participant has a go at walking on custard—he starts off so well.

To celebrate this Birmingham/pharmacy heritage, we filled two children's paddling pools each with 40 litres of cold Bird's custard (which was in essence a suspension of corn flour), and we also had several 10-litre beakers of tomato ketchup for comparison. The 30 litres of ketchup was easy to obtain, but the 100 kg of cornstarch did prove more difficult, but eBay really is amazing—next day free delivery, fabulous. Dan Kirby, who led our team in setting up this part of our exhibit, was the first to test whether we could indeed walk on our custard, and after his initial proof of concept, it was impressive to see nearly as many adults as children taking up the challenge and walking on custard. Well, when we say walk, it was more of a jog to avoid sinking.

Exploring densities formed a second part of our exhibit, and Sarah McNeil set this up for us. We had planned this to be less messy but alas not; the chance to stack liquids of decreasing density on top of each other was a good challenge, with most children doing well; however we did end up getting syrup everywhere and had to stop a few more adventurous participants from testing what would happen if they poured these mixtures into the custard.

There were also a few other questions we addressed throughout the day. Did you know that a can of Coke sinks in water but a can of Diet Coke floats? Honestly it does, just shows how much sugar Coke contains. Also, if you place an unpeeled orange in a bowl of water it floats, but if you peel the orange it sinks.

Behfar with some of the "stacking solutions" the children made.

Diet versus regular Coke.

All in all, the day went really well, with lots of kids getting to explore science and then learn a little more about medicines; you never know, some may be our future CRS members. We got lots of positive feedback, and only one grumpy man complained about almost slipping on custard (which as any of the kids who participated could have told him could not possibly happen due to the shear thickening properties of the custard). Clearly our exhibit was not to his taste. ■

People in the News

Compiled by Steven Giannos
Industrial Editor

Professor Leroux from ETH Receives the Debiopharm Life Sciences Award 2010

PRNewswire: September 2, 2010 – LAUSANNE, SWITZERLAND – Debiopharm Group, a Swiss-based global biopharmaceutical group of companies with a focus on the development of innovative prescription drugs that target unmet medical needs, has named Prof. Jean-Christophe Leroux as the recipient of the Debiopharm Life Sciences Award 2010 for his innovative research on polymer chemistry, nanotechnology, and pharmaceutical sciences to yield novel drug therapies. This year, the theme for the award was "Drug Delivery and Pharmaceutical Technology." Prof. Leroux is an expert in galenic studies at the Swiss Federal Institute of Technology (ETH) in Zurich. He and his institute received CHF 100,000. Funded by Debiopharm, the ceremony took place at the EPFL (Ecole Polytechnique Federale de Lausanne) during the EPFL School of Life Sciences Symposium "Engineering Life."

"We congratulate Professor Leroux for his outstanding research," said Rolland-Yves Mauvernay, president and founder of Debiopharm Group. "A panel of experts from Debiopharm and the EPFL examined many high-level and promising applications from all over Europe; our decision to nominate Professor Leroux was unanimous. We were seduced by his innovative research, his general expertise and broad overall knowledge in drug delivery. The application file submitted by Professor Leroux was very comprehensive, with an impressive list of publications in high-impact factor pharmaceutical, materials and biomedical journals. He is a leading figure in an area that is likely to revolutionise medical therapeutics in the years to come."

The development of suitable drug formulations and delivery systems remains a major challenge in the full drug product development and industrialization process. In his applied research, Prof. Leroux is interested in the design of new carriers and materials for various pharmaceutical applications, such as drug detoxification and the treatment of celiac disease (intolerance to gluten). Currently different approaches are being assessed as supportive treatments of celiac disease. The polymeric binder technology that was developed in his laboratory will be further investigated. In parallel, he will examine another known strategy to study the stability of enzymes (exogenous propyl endopeptidases) in the gastrointestinal tract and try to improve it with various new polymers. He will also elaborate imaging tools to study in real time enzymatic activity *in vivo*. Prof. Leroux's more fundamental research aims to better understand how antisense oligonucleotides (ONs) and small interfering ribonucleic acids (siRNAs) are naturally taken up by cells and to discover ways by which he may enhance this phenomenon. The identification and exploitation of these uptake mechanisms have the potential to change our way of thinking about delivery of siRNAs and to provide the basis for developing novel strategies for medicines based on RNA interference.

Prof. Leroux earned his B.Pharm. degree from Montreal University (1992) and his Ph.D. degree from Geneva University (1995). He has held various positions at the Faculty of Pharmacy at Montreal University, from assistant professor to adjunct professor. Since 2008, Prof. Leroux has headed the laboratory of Drug Formulation and Delivery at the Institute of Pharmaceutical Sciences at the Swiss Federal Institute of Technology (ETH) in Zurich. He is among the major experts on liposomes and nanotechnologies in medicine and is a member of CRS. ■

In the News

Compiled by Steven Giannos
Industrial Editor

October 2010

Rapid Absorption Rate Alone May Not Explain Efficacy in Migraines of Sumatriptan Delivered with OptiNose's Novel Drug Delivery Technology

Business Wire: October 28, 2010 – YARDLEY, PA – OptiNose Inc. has announced the results from an analysis comparing the Phase II clinical trial of its novel delivery technology to that of other formulations. The analysis suggests rapid absorption rate alone may not explain the efficacy in migraines treated with sumatriptan delivered with the company's novel bi-directional technology.

The data highlight the technology's ability to offer the dual benefits for migraine sufferers of rapid onset of pain relief and sustained pain freedom. When comparing existing pharmacokinetic and pharmacodynamics data from various formulations of sumatriptan, it appears the rate of absorption alone does not explain differences in rates of headache relief.

"It has been previously documented that the OptiNose nasal powder device offers improved deposition in the nasal cavity of sumatriptan to segments innervated by the first and second trigeminal nerve branches," said Per G. Djupesland, M.D., Ph.D., chief scientific officer (CSO) of OptiNose and inventor of the company's bi-directional delivery technology. "We speculate the significant clinical effects of OptiNose sumatriptan powder in migraine are in part due to blocking of pain signaling in the trigeminal nerve, widely considered to be a primary source of migraine pain."

The 2007 US Migraine Prevalence and Prevention study revealed the 1-year prevalence is more than 17% for women and nearly 6% for men. In addition, according to the World Health Organization (WHO), migraine is in the top 20 causes of disability worldwide. This clinical trial assessed 117 adult patients with migraines of moderate or severe intensity. The patients were randomly to one of three treatment groups: 10 mg of sumatriptan, 20 mg of sumatriptan, or placebo. Highlights of the randomized, double-blind, placebo-controlled, dose-ranging, parallel group study include

- A significantly greater proportion of subjects in both the 10 mg of sumatriptan (54%) and 20 mg of sumatriptan (57%) groups were pain free at 120 min compared with placebo (25%).
- For both the 10-mg (73%) and 20-mg (74%) sumatriptan doses, the proportion of patients with relief of headache was significantly greater than placebo (38%) at 60 min.
- The median time to meaningful relief was 54 min for 10 mg of sumatriptan and 50 min for 20 mg of sumatriptan, with both times significantly faster than the median time of 120 min for placebo.
- There were marked reductions in the incidence of nausea, photophobia, and phonophobia compared with baseline in both the 10 and 20 mg of sumatriptan groups between 60- and 120-min post-dose.

"These results suggest the activity of sumatriptan can go beyond what is delivered traditionally via oral ingestion if the medication can be delivered to the right place and in the right amount," Djupesland said. "Further research is needed to explore the hypothesis that the improved delivery of medication with the OptiNose technology is blocking pain by direct actions on or via the trigeminal nerve, however these are certainly intriguing results." OptiNose will be initiating a Phase III development program within the next year to further evaluate the efficacy and safety of sumatriptan delivered via its technology.

BioDelivery Sciences Announces Positive End-of-Phase II Meeting with FDA for BEMA Buprenorphine for Chronic Pain

Business Wire: October 27, 2010 – RALEIGH, NC – BioDelivery Sciences International, Inc. (Nasdaq: BDSI) has announced a positive End-of-Phase II meeting with the U.S. Food and Drug Administration (FDA) that took place on September 14, 2010. At that meeting, agreement was reached on the BEMA buprenorphine development plan for the treatment of chronic pain. As a result, the Phase III clinical program evaluating the efficacy and safety of BEMA buprenorphine for the treatment of moderate to severe chronic pain will be initiated this quarter.

"We are very pleased with the outcome of our End-of-Phase 2 meeting with FDA where clear guidance was provided on our development requirements for BEMA buprenorphine," stated Dr. David Wright, vice president of regulatory affairs at BDSI. "There were no surprises, and we are moving forward into Phase 3."

According to Dr. Andrew Finn, executive vice president of product development at BDSI, "Given our clinical and regulatory success with the execution of the ONSOLIS program, we are confident in our ability to efficiently execute this program as planned. Driven by patient enrollment and retention, results could be expected as early as the third quarter of 2011, allowing for a potential NDA filing in the first half of 2012. We hope to be the first oral transmucosal form of buprenorphine for the treatment of pain to be approved for use in the U.S."

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TransPharma Announces Successful Results of a Phase I Clinical Trial of Its New Self-applied ViaDerm System for the Treatment of Osteoporosis

Business Wire: October 26, 2010 – LOD, ISRAEL – TransPharma Medical Ltd., a specialty pharmaceutical company focused on the development and commercialization of drug products utilizing a proprietary active transdermal drug delivery technology, has announced the successful results of a 4-week Phase I trial of its new self-applied ViaDerm-hPTH(1-34) for the treatment of osteoporosis.

This study, sponsored by Eli Lilly and Company in collaboration with TransPharma Medical, was a subject and investigator, blind placebo-controlled, dose-escalation study of 60 healthy postmenopausal Japanese women designed to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of hPTH(1-34) (known as Forteo in its injected form). hPTH(1-34) was either administered at the investigation site or self-administered at home for a total of 28 days in transdermal doses of 30, 50, and 80 µg via the ViaDerm system compared to daily 20-µg Forteo injections.

The results of the study demonstrate ViaDerm-hPTH(1-34) to be safe and well-tolerated, with PK and PD (bone biomarkers) dose responses corresponding to the escalating hPTH(1-34) doses of the ViaDerm patches. The PK and PD results related to the postmenopausal Japanese women were consistent with former ViaDerm-hPTH(1-34) Phase I and Phase IIa studies conducted in non-Japanese subjects with comparable doses at other locations around the world. TransPharma's new self-applied ViaDerm system has been used successfully by healthy Japanese postmenopausal women and has performed similarly to that of the company's previous system, which had to be applied to the patient. This 4-week study was carried out in parallel to a 12-month, multi-site, Phase IIb study currently being conducted in Central and South America and Europe.

"We are very pleased with the results of this study, in which we successfully demonstrated the performance of our new self-applied ViaDerm system as a product intended for home use," said Dr. Daphna Heffetz, CEO of TransPharma Medical. "This is an important step towards introducing the ViaDerm system as a household solution for the self-delivery of a variety of medical substances, first and foremost being hPTH(1-34) for the treatment of osteoporosis." For more information, please visit the company's website at www.transpharma-medical.com.

Agile Therapeutics Announces Study Results Demonstrating Contraceptive Patch AG200-15 Delivers a Low Dose of Estrogen

Business Wire: October 26, 2010 – PRINCETON, NJ – Agile Therapeutics has announced the results from a Phase II clinical study of AG200-15, Agile's weekly contraceptive patch containing ethinyl estradiol (EE) in combination with levonorgestrel (LNG). According to the clinical findings, AG200-15 provides a low daily dose of estrogen equivalent to 30 µg of EE, similar to that in low-dose, oral contraceptive (OC) pills. The study findings were delivered in an oral presentation at the American Society for Reproductive Medicine (ASRM) 66th Annual Meeting.

AG200-15 incorporates Agile's proprietary SKINFUSION™ transdermal delivery technology and is applied once weekly for 3 weeks followed by a patch-free week. Agile also has announced the completion of patient enrollment ahead of schedule in its pivotal Phase II NEW CHOICE study of AG200-15.

Dr. Marie Foegh, chief medical officer and vice president, clinical research and development, of Agile Therapeutics, stated, "The reported Phase 2 results demonstrate AG200-15 delivers a dose of estrogen sufficiently low to avoid increased risk of adverse events, but still effective in preventing unwanted episodes of breakthrough (nonscheduled) bleeding. We believe this innovation, delivering the right dose of estrogen in combination with levonorgestrel, can address women's desire for greater safety, convenience and ease of compliance in their choice of hormonal contraception."

Al Altomari, Agile president and CEO, commented, "The daily estrogen exposure demonstrated in the Phase 2 study confirms our estimates based on the dose-ranging studies performed earlier by Agile. This is the first head-to-head study with a contraceptive patch vs. an OC to demonstrate EE exposure comparable to a low dose OC. We have designed AG200-15 to answer the market need for a contraceptive patch that provides convenience and compliance, with a low-dose of estrogen."

Altomari continued, "Previous studies have demonstrated that AG200-15 is well-tolerated with a favorable breakthrough bleeding profile, very low rates of irritation, and adhesion in real-world conditions over the 7-day period of application. Agile's patch is an elegant solution to meet the promise of contraceptive patch technology."

Agile's Phase II open-label, crossover study compared the EE pharmacokinetic (PK) profile of AG200-15 to an oral contraceptive in healthy female volunteers. Thirty-two subjects were included in the analyses. The maximum plasma concentration level (C_{Max}) was approx. 60% lower for AG200-15, and steady state concentration levels (C_{ss}) were 15–20% lower for AG200-15 compared to 35 µg of OC ($P < 0.02$).

According to the oral presentation at ASRM, "Daily EE exposure with the novel, low-dose transdermal contraceptive delivery system AG200-15 is comparable with that of a low-dose OC." The daily dose of AG200-15 is approx. 30 µg of EE and is well within the range reported for low-dose OCs.

Photovoltaic Medicine: Miniature Solar Cells Might Make Chemotherapy Less Toxic

ScienceDaily: October 25, 2010 – EL PASO, TX – Micro-scaled photovoltaic devices may one day be used to deliver chemotherapeutic drugs directly to tumors, rendering chemotherapy less toxic to surrounding tissue. "In the first step,

we were able to prove the concept," says Tao Xu, Ph.D., an assistant professor at the University of Texas in El Paso. Xu and his colleagues presented their findings at the AVS 57th International Symposium & Exhibition.

Currently, chemotherapeutic drugs are piped through an IV drip into the bloodstream, where they travel and come in contact with many organs on the way to their target. Patients are affected systemically, with toxic side effects that are well known. Ideally, clinicians would like to have a way to deliver these powerful drugs only where needed—to target them specifically to tumor tissue. Xu's device is designed to do just that—release drug only when stimulated by light, focusing it directly on a tumor during treatment. Near infrared or laser light is believed to penetrate tissues over 10 cm deep.

The novel device converts light into electric current. In an *in vitro* model system, positively or negatively charged "model" drugs were used to coat opposite sides of the miniature solar cell. Upon introduction of a light beam, one side of the device became positively charged, repelling the positively charged molecules the investigators had placed there, releasing them; the same thing happened with the negatively charged side and negative model molecules.

It appears that "our hypothesis will work," said Xu, who added that the amount of drug released can also be controlled by varying the intensity of light. The first phase employed an *in vitro* model; according to Xu, the next step for the work would be its application in small animal models.

Inovio Pharmaceuticals' Minimally Invasive DNA Vaccine Delivery Device Featured in the Journal *Gene Therapy*

Business Wire: October 25, 2010 – BLUE BELL, PA – Inovio Pharmaceuticals, Inc. (NYSE Amex: INO), a leader in the development of therapeutic and preventive vaccines against cancers and infectious diseases, has published a peer-reviewed research article describing the development of a new intradermal, minimally invasive DNA vaccine delivery device in the prestigious journal *Gene Therapy*. This very low-voltage device, which does not penetrate the skin, further enhances the previously established tolerability of Inovio's electroporation devices. Moreover, DNA vaccines delivered using this device produced strong antibody and T-cell immune responses and achieved protection from lethal challenge in multiple animal models, including non-human primates. The lead author of the paper, "Prototype Development and Preclinical Immunogenicity Analysis of a Novel Minimally Invasive Electroporation Device," is Dr. Niranjan Y. Sardesai, senior vice president, research and development. Other collaborators include Dr. David B. Weiner, chair of Inovio's Scientific Advisory Board and professor, Department of Pathology & Laboratory Medicine, University of Pennsylvania.

Inovio's new minimally invasive intradermal device is based on its electroporation delivery platform, in which controlled, millisecond electrical pulses create permeability in cell membranes and enable dramatic uptake of biological material previously injected into targeted muscle or skin tissue. Inovio's electroporation systems have been shown to increase cellular uptake of a DNA vaccine 1,000-fold or more and to increase levels of gene expression (production of the antigen coded by the DNA vaccine) and immune responses to the antigen up to 100-fold.

While current Inovio electroporation devices have been shown to be safe and well-tolerated in multiple human studies, Inovio has been advancing research into more portable and patient-friendly next-generation delivery devices. In this context, the study reported in *Gene Therapy* used voltages averaging roughly seven times less than its current devices. The paper noted that the use of non-penetrating needle electrodes and lower-voltage parameters encompassed in this device concept further improves the tolerability of this delivery platform. By enabling simple delivery into the skin, this device can serve to expand applications for DNA delivery in humans to broader prophylactic settings, i.e., for mass vaccinations, and may extend the range of immunizations to both older and younger populations. This new device also facilitates the delivery of more complex formulations and antigen mixtures that may better address targeted diseases.

The authors investigated the delivery of candidate influenza DNA vaccines, demonstrating that DNA delivered intradermally via the minimally invasive (equivalent to a slight scratch of the skin), low-voltage device conferred 100% protection in a mouse model to the vaccinated animals against a lethal challenge of influenza H5N1. Influenza DNA vaccine delivered via the device also produced HA-inhibition (HAI) titers significantly over 1:40 in two other large animal models, including in non-human primates. While these large animals were not subsequently challenged in this study, titers greater than 1:40 are considered to be protective in the influenza model in a number of species.

Dr. J. Joseph Kim, CEO of Inovio Pharmaceuticals, said, "Inovio is the clear leader in DNA vaccine development and delivery. This important study unveils our exciting, next generation minimally-invasive drug delivery technology and enables the development of a new generation of preventive vaccines against many challenging diseases and for a broad spectrum of the population. We look forward to continuing our R&D leadership in this field."

Diamyd Medical Divides Operations into Two Business Areas: Diabetes and Pain

Business Wire: October 22, 2010 – STOCKHOLM, SWEDEN – In her year-end report, Elisabeth Lindner, president and CEO of Diamyd Medical, states that the company has decided to divide its operations into two business areas beginning with the new 2010/2011 fiscal year: diabetes and pain. The diabetes business area consists of the antigen-based candidate drug Diamyd® for the treatment and prevention of autoimmune diabetes. The pain business area consists of develop-

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ment projects that use the company's proprietary NTDDS (nerve-targeting drug delivery system) platform to administer drugs directly to the nervous system to treat pain.

"We have decided to divide our operations in order to highlight our pain portfolio. We see a great medical need and an opportunity to quickly demonstrate the value of our pain portfolio by continuing our cancer pain program with NP2 Enkephalin. In addition to NP2 Enkephalin, Diamyd currently has two more candidate drugs in business area Pain: NG2 GAD and NE2 Endomorphin, creating good prospects for the further development of a competitive product portfolio in the area of pain," stated Elisabeth Lindner, CEO and president of Diamyd Medical.

During the fourth quarter Diamyd signed an agreement with Ortho-McNeil-Janssen Pharmaceuticals, Inc. (OMJPI) to develop and commercialize the Diamyd® diabetes therapy. Diamyd has secured exclusive rights for commercialization in the Nordic countries with the objective to build a small pharmaceutical company with its own development operations and a sales and marketing organization in the Nordic countries.

Diamyd has reported promising safety findings from a Phase I study on chronic pain with the candidate drug NP2 Enkephalin. Substantial and sustained reduction in pain scores were reported in the middle- and high-dose cohorts treated with NP2 Enkephalin.

Apricus Bio Announces First Patent Grant for Femprox® in Japan

Business Wire: October 18, 2010 – SAN DIEGO, CA – Apricus Biosciences, Inc. (Nasdaq: APRI), backed by a revenue-generating CRO business and seeking to leverage its multi-route NexACT® drug delivery technology and internal pipeline through out-licensing partnerships, announced that the Japanese Patent Office has issued a decision to grant a patent for the company's application on Femprox®, entitled "Compositions and Methods for Amelioration of Human Female Sexual Dysfunction." This patent, when issued, will provide Japanese patent protection until December 2019 and is one in a series of patents and pending applications that Apricus Bio owns on Femprox® and the underlying NexACT® technology.

Commenting on the news, Dr. Bassam Damaj, president and chief executive officer of Apricus Bio, stated, "We are very pleased with our first patent allowance for Femprox® in Japan. We continue to aggressively pursue intellectual property ("IP") coverage for our technology and product candidates under development and this allowance adds to the strength of our overall IP position. In addition to the newly allowed claims in Japan, we have corresponding coverage and protection for Femprox® in many other major international markets. The advancement of our patent portfolio comes at an optimal time, as we are in active discussions with potential partners to out-license Femprox®."

Femprox® is an alprostadil-based cream intended for the treatment of female sexual arousal disorder. Apricus has completed nine clinical studies to date, including one, 98-patient Phase II study in the United States and a 400-patient proof-of-concept Phase II/III study in China, where the cost for conducting clinical studies is significantly lower than in the United States.

Alkermes Announces FDA Approval of VIVITROL for Prevention of Relapse to Opioid Dependence

Business Wire: October 12, 2010 – WALTHAM, MA – Alkermes, Inc. (NASDAQ: ALKS) announced that the U.S. Food and Drug Administration (FDA) has approved VIVITROL (naltrexone for extended-release injectable suspension) for the prevention of relapse to opioid dependence, following opioid detoxification. VIVITROL is now the first and only non-narcotic, non-addictive, once-monthly medication approved for the treatment of opioid dependence. VIVITROL was approved by the FDA in 2006 for the treatment of alcohol dependence and should be used as part of a comprehensive management program that includes psychosocial support.

"Opioid dependence is a serious and chronic illness characterized by high rates of relapse," stated Dr. Marc Fishman, assistant professor of psychiatry, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine. "VIVITROL is an opioid-blocking medication that offers patients and physicians a once-monthly medication to prevent relapse to opioid addiction."

"As an organization that helps families find treatment and offers support for loved ones with addiction, we see firsthand that opioid dependence is one of the most significant health issues facing our nation. This new indication for Alkermes' product as a non-addictive approach to prevent relapse to opioid dependence brings new hope to the families we serve," said Steve Pasierb, president and chief executive of The Partnership at Drugfree.org.

"Opioid dependence is a growing disease and we believe that VIVITROL offers physicians and their patients a whole new approach, as the only long-acting, non-addictive treatment for opioid dependence," stated Richard Pops, chief executive officer of Alkermes. "We look forward to helping to improve the lives of patients with this chronic and debilitating condition."

The FDA approval of VIVITROL for the prevention of relapse to opioid dependence was based on data from a 6-month, multicenter, randomized Phase III study that met its primary efficacy endpoint and all secondary efficacy endpoints. Data from the intent-to-treat analysis showed that patients treated once a month with VIVITROL demonstrated statistically significant higher rates of opioid-free urine screens compared with patients treated with placebo ($P < 0.0002$). VIVITROL was generally well tolerated in the study. The most common clinical adverse events experienced by patients receiving VIVITROL during the study were hepatic enzyme elevations, nasopharyngitis, and insomnia.

For more information, please visit www.vivitrol.com or call +1.800.VIVITROL (+1.800.848.4876).

Columbia Laboratories Announces USPTO Notice of Allowance for Key Progesterone Preterm Birth Patent

Business Wire: October 12, 2010 – LIVINGSTON, NJ – Columbia Laboratories, Inc. (Nasdaq: CBRX) announced that the U.S. Patent and Trademark Office (USPTO) has issued Watson Pharmaceuticals, Inc. (NYSE: WPI) a notice of allowance for a key patent for the use of progesterone to treat or prevent preterm birth. The USPTO issues a notice of allowance to report that a patent application has been examined and is allowed for issuance as a patent. The patent is expected to issue within three months upon payment of required fees.

The new patent pertains to the use of progesterone to treat women with a short cervix at mid-pregnancy to prevent spontaneous preterm birth. A short cervix at mid-pregnancy is the single most important predictor of preterm birth. The patent will cover CRINONE and PROCHIEVE (progesterone gels) and any next-generation products in the potential new preterm birth indication until at least February 2028. The patent application was among the assets Columbia sold to Watson in July 2010.

"This use patent, which is founded in our longstanding research efforts in preventing preterm birth, will help safeguard our future royalty stream from Watson Pharmaceuticals for progesterone products in the potential preterm birth indication," said Frank C. Condella, Jr., Columbia president and chief executive officer. "We look forward to reporting results of the PREGNANT Study, our pivotal Phase III clinical trial of PROCHIEVE to reduce the risk of preterm birth in women with a short cervix at mid pregnancy, in December."

Inviragen and PharmaJet Receive $15.5 Million NIAID Contract to Develop a Needle-free Dengue Vaccine

Business Wire: October 7, 2010 – FORT COLLINS, CO, and GOLDEN, CO – Inviragen and PharmaJet have been awarded a five-year, $15.5 million contract from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), to advance the development of a needle-free, easy-to-administer dengue vaccine. The award will fund preclinical studies, regulatory filings, manufacturing, and clinical testing of Inviragen's tetravalent dengue vaccine, DENVax, delivered with PharmaJet's convenient needle-free injection device.

"This NIAID contract will allow Inviragen and PharmaJet to continue our pioneering development of a needleless dengue vaccine," commented Dr. Dan Stinchcomb, Inviragen chief executive officer. "The PharmaJet injector has many properties that make it ideal for administering a dengue vaccine worldwide, potentially saving lives in affected countries and reducing the spread of the disease to new regions."

Over 3.5 billion people live in countries that have frequent dengue outbreaks. The four dengue viruses are spread among humans by mosquitoes and cause an estimated 30–50 million cases of debilitating dengue fever and 0.5–2 million cases of life-threatening dengue hemorrhagic fever every year. A recent dengue outbreak in Florida highlights the continuing global spread of the disease.

"People of all ages fear needles and safe disposal of needle waste is a constant problem for health care providers. A needle-free dengue vaccine would be welcomed by patients in endemic countries and by travelers worldwide and could protect them from this devastating disease," said Dr. Linda McAllister, PharmaJet interim chief executive officer. "In this collaboration, PharmaJet will develop 'needle-free' syringes compatible with our jet injection technology for pre-filling with Inviragen's novel dengue vaccine."

Inviragen's DENVax vaccine, developed by researchers at the CDC's Division of Vector-borne Diseases, is based on an attenuated DEN-2 virus that generates long-lasting anti-dengue immune responses. CDC scientists engineered this clinically tested, weakened DEN-2 virus to express DEN-1, DEN-3, or DEN-4 structural genes. DENVax is a four-way mixture of the three engineered viruses and the original DEN-2 strain. Inviragen has completed preclinical testing, formulation, and manufacturing of DENVax. Phase I clinical safety testing of DENVax, delivered by traditional needle and syringe, began earlier this year. Other dengue vaccine technologies in clinical testing require multiple injections with long intervals between doses. The goal of the Inviragen/PharmaJet collaboration is to develop a needle-free dengue vaccine delivery platform that can rapidly induce neutralizing antibody response after one or two easily administered doses.

PharmaJet's jet injector creates a fine stream of pressurized liquid that penetrates the skin, quickly and effectively delivering doses of medicines and vaccines into different tissues. Jet injection eliminates needles from the process of administering vaccines and eliminates the costs and dangers associated with sharp needle waste. PharmaJet's technology is FDA-cleared for delivery into the muscle (intramuscular) and under the skin (subcutaneous). PharmaJet is developing jet injectors for delivery between the skin layers (intradermal). For some vaccines, intradermal delivery has the potential to reduce the amount of vaccine required, leading to cost savings and expanded coverage for vaccines in limited supply.

"In preliminary animal model studies, we used PharmaJet technology to deliver DENVax intradermally. The combination was safe, induced neutralizing antibodies to all four dengue serotypes and protected against dengue infection," noted Dr. Jorge Osorio, Inviragen chief scientific officer. "Our ongoing Phase 1 clinical trial is assessing the safety and immune responses after both subcutaneous and intradermal delivery of DENVax by needle. Under this NIAID contract, we aim to test DENVax delivery with the PharmaJet device in children and adults in South America and Southeast Asia, regions that are significantly impacted by dengue disease."

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Noven Completes Acquisition of Daytrana Methylphenidate Transdermal System (CII) from Shire

Business Wire: October 1, 2010 – MIAMI, FL – Noven Pharmaceuticals, Inc. has completed the acquisition of global rights to Daytrana (methylphenidate transdermal system) from affiliates of Shire plc. Daytrana was originally licensed globally to Shire by Noven in 2003 and was approved and launched in the United States in 2006. The product is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 to 17 years old. Daytrana should be used as part of a total treatment program for ADHD that may include counseling or other therapies. Shire's net sales of the product for the first half of 2010 were $34.7 million.

Daytrana will be marketed and sold by Noven Therapeutics, Noven's specialty pharmaceuticals marketing and sales unit. Noven Therapeutics currently promotes the oral prescription products Pexeva, Stavzor, and Lithobid to psychiatrists and other appropriate physicians in the United States. Daytrana product availability will not be interrupted or otherwise affected by the acquisition or by the transfer of the product to Noven.

Jeffrey Eisenberg, Noven president and chief executive officer, said, "We are very pleased to complete the acquisition and to add Daytrana—a product developed and manufactured by Noven—to the portfolio of products that we market and sell through Noven Therapeutics. I extend my thanks and appreciation to Shire for their partnership and support during the period of their license of Daytrana, and to both the Noven and Shire teams who made the transaction happen. Daytrana continues to represent an important therapeutic option in the treatment of ADHD. As an organization, we're excited to begin active promotion of the product, with the goal of increasing awareness of Daytrana and helping patients, physicians and caregivers manage the symptoms of ADHD."

Applied Pharma Research s.a. (APR) and Labtec GmbH Enter into Exclusive Licensing Agreement with Ferrer Internacional for Donepezil Oral Dispersible Film

Business Wire: October 1, 2010 – BALERNA, SWITZERLAND, and BARCELONA, SPAIN – APR and its development partner Labtec have entered into an exclusive licensing agreement with the leading European pharmaceutical company Ferrer Internacional for the promotion, distribution, and marketing of Donepezil oral dispersible film (ODF) in Spain, Portugal, and Germany. Terms of the deal were not disclosed.

"It is an honor to work with a dedicated and professional company like APR. Donepezil Rapidfilm with its unique delivery system will be part of Ferrer's CNS portfolio and is in line with our overall aim to bring new treatment alternatives for our patients," said José Luis Fumanal, Ferrer vice president of domestic operations, pharma. "As Ferrer has a successful track record in licensing collaborations, we are convinced that the current agreement with APR will be the initiation of another long-lasting partnership strengthening our supportive care line for our patients."

"Market trends are clear," said Paolo Galfetti, APR CEO. "The future of many molecules to become off-patent such as Donepezil will be determined by dosage form diversification and patient compliance. ODF certainly is the oral dosage form contributing the most to compliance by ensuring drug delivery while being easy to use without any discomfort for patients and doctors. We are also very pleased that such a reputable company as Ferrer Internacional took the Donepezil ODF opportunity for such key markets in Europe. I would also like to express my appreciation for the great co-operation we had from Bioselenia, our strategic licensing partner, that helped to build the connection between APR and Ferrer Internacional on this deal."

Donepezil ODF is an innovative oral thin film formulation for the symptomatic treatment of Alzheimer's disease and other types of dementia. Donepezil is one of the top-selling molecules in its class of drugs. Donepezil ODF consists of a thin film strip based on a water-soluble polymer. The film disintegrates on contact with water or saliva within seconds, releasing the drug in the mouth and promoting gastrointestinal absorption. The patient does not have any swallowing difficulty, and dosage delivery is ensured since the film immediately melts once it is put on the tongue.

Following Ondasetron ODF, Donepezil ODF is the second licensed candidate of a broad development pipeline of ODF prescription products based on APR/Labtec's proprietary Rapidfilm technology. The eCTD dossier of the product is expected to be completed by the end of 2010 to start the registration process in Europe. The product will be manufactured by Labtec.

Targeting primarily pain and CNS indications, other licensing candidates include Zolmitriptan and the blockbuster molecule Olanzapine.

September 2010

Data Monitoring Committee Recommends Continuation of Celsion's Phase III ThermoDox HEAT Study to Treat Primary Liver Cancer

PRNewswire-FirstCall: September 30, 2010 – COLUMBIA, MD – Celsion Corporation (Nasdaq: CLSN), a leading oncology drug development company, announced that after reviewing data from 401 patients enrolled in its pivotal Phase III ThermoDox clinical study (the HEAT study) for primary liver cancer, the Data Monitoring Committee (DMC) has unanimously recommended that the trial continue to enroll patients with the goal of reaching the 600 patients required to complete the study. The company previously announced that the U.S. Food and Drug Administration (FDA) designated the HEAT study of its investigational drug ThermoDox, in combination with radiofrequency ablation (RFA), as a fast track development program. ThermoDox, a proprietary heat-activated liposomal encapsulation of doxorubicin, is currently being evaluated under a special protocol assessment (SPA) agreement with the FDA in this global Phase III trial in patients with non-resectable hepatocellular carcinoma (HCC), commonly referred

to as primary liver cancer. With nearly 75% of patients enrolled in the trial, Celsion's target is to complete patient enrollment over the next 4 months. As a part of its commitment to Japan's PMDA, the DMC will continue to independently assess safety in patients randomized at Japanese sites. The goal is to provide data from this cohort sufficient to support immediate registration in Japan following a successful study.

The DMC for the HEAT study is composed of an independent group of medical and scientific experts with the responsibility for reviewing and evaluating patient safety and efficacy data from the company's Phase III ThermoDox HEAT study. The DMC reviews study data at regular intervals, with their primary responsibilities being to ensure the safety of all patients enrolled in the trial, the quality of the data collected, and the continued scientific validity of the trial design. The trial design and statistical plan for the HEAT study also incorporate a pre-planned interim efficacy analysis by the DMC (after patient enrollment is complete and 190 progression-free survival events are realized in the study population), with the intent of evaluating safety and efficacy results to determine if there is overwhelming evidence of clinical benefit or a low probability of treatment success (a futility analysis) to continue, modify, or terminate the trial.

"We are very pleased that the DMC has unanimously recommended continuation of the HEAT study based on its review of all available clinical data, both safety and efficacy, in over 400 patients," stated Michael H. Tardugno, Celsion president and chief executive officer. "The DMC's affirmative review is further evidence of ThermoDox's potential to provide a first line of chemotherapy for the treatment of primary liver cancer."

The National Institutes of Health and regulatory agencies around the world, as well as the liver cancer medical community, have all recognized the potential of ThermoDox for the treatment of this unmet medical need, as evidenced by the following:

- The HEAT study is being conducted under a special protocol assessment with the FDA
- The HEAT study has been granted a fast track designation by the FDA
- The National Cancer Institute recently designated the HEAT study as a priority clinical trial at its recent Clinical Trial Planning Meeting for HCC.

Access Pharmaceuticals Furthers Progress on Its Cobalamin-Mediated Targeted Drug Delivery Platform for siRNA

PRNewswire: September 29, 2010 – DALLAS, TX, and NEW YORK, NY – Access Pharmaceuticals, Inc. (OTC Bulletin Board: ACCP), a biopharmaceutical company leveraging its proprietary drug-delivery platforms to develop treatments in areas of oncology, cancer supportive care, and diabetes, announced that it has made significant progress with its proprietary Cobalamin-targeted drug-delivery program for siRNA therapies. As a result of the continued advancements made with its Cobalamin program, Access rebranded the targeted-drug delivery technology as CobaCyte and submitted additional patent applications for its improved CobaCyte formulations, including siRNA compositions.

Over the past months, Access' CobaCyte siRNA application has shown significant promise. In an *in vitro* siRNA transfection dose-response study, Access' CobaCyte nanoparticle carriers loaded with an apoptosis-inducing siRNA molecule showed transfection activity in hard-to-transfect cell lines with potentially better toxicity profiles compared with other reagents. Further studies, including *in vivo* gene-knockdown studies, are planned. Additionally, Access has initiated a program whereby proprietary formulations of currently marketed chemotherapies will be developed and tested to assess CobaCyte's ability to enhance drug pharmacokinetics and pharmacodynamics.

"We're excited about the early progress and results seen in our CobaCyte-targeted drug-delivery activities, especially in the area of siRNA," stated Jeffrey B. Davis, president and CEO of Access Pharmaceuticals. He continued, "The new patent filings and the branding of the CobaCyte name will help enhance and facilitate our corporate partnering activity in this area."

"Access and its collaborators have demonstrated that our CobaCyte carrier nanoparticles can get siRNA molecules in cells, and that we can impact transfection efficiency by varying the loading of vitamin B-12, our principle targeting agent," commented David P. Nowotnik, senior vice president, research and development. He continued, "Based on our collective work with current and previous formulations using the CobaCyte approach, we believe we have the right scientific basis in place for the future development of CobaCyte RNAi therapeutics."

RNAi is typically initiated by the introduction of small fragments of RNA, termed siRNA, into cells at disease sites. Due to their large size and high negative charge, siRNA fragments are not able to cross cell membranes. Therefore, to develop effective RNAi therapeutics, a delivery system must be developed that can transport the siRNA into cells and release undamaged siRNA into target cell cytoplasm. The CobaCyte technology is particularly well-suited for this purpose. Most human cells have a requirement for vitamin B_{12} that is served by cell surface receptors that facilitate absorption of this vitamin. In many diseases, the demand for vitamin B_{12} is increased, with a corresponding upregulation of the receptor. Using the Trojan Horse principle, the CobaCyte nanoparticle technology can utilize the vitamin B_{12} uptake mechanism to transport siRNA into cells, whereupon native siRNA can be released for incorporation in messenger RNA (mRNA) to initiate the beneficial therapeutic effect. In this way, CobaCyte offers the potential for targeted delivery of siRNA. The fact that Access' vitamin B_{12} technology also facilitates oral drug delivery indicates that it may be possible for this technology to provide effective siRNA treatments by oral drug delivery.

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Generex Awarded a New Patent in Canada for Its Proprietary Buccal Drug Delivery System

PRNewswire: September 28, 2010 – WORCESTER, MA – Generex Biotechnology Corporation (Nasdaq: GNBT), the leader in drug delivery for metabolic diseases through the inner lining of the mouth, has been awarded a new patent in Canada. The Canadian Intellectual Property Office granted Canadian Patent 2,401,942, "Pharmaceutical Compositions for Buccal and Pulmonary Application." This new patent increases the number of issued patents related to the company's buccal drug delivery platform technologies to 161. A total of 102 patent applications remain pending.

"We are pleased that we continue to establish the inventiveness of the Company's buccal delivery system as there has been relatively little progress over the years in reaching the target of safe and effective oral formulations for macromolecules, including peptides and proteins," stated Rose C. Perri, Generex chief operating officer. "We are pleased that we continue to receive patents from key markets within which our delivery system can be commercialized with a pipeline of viable applications that will open up other marketplaces for the Company."

Intarcia Presents Positive ITCA 650 Phase II Study Results for Type 2 Diabetes at EASD

PRNewswire: September 22, 2010 – HAYWARD, CA – Intarcia Therapeutics, Inc. has presented the final results of a 24-week Phase II clinical study of ITCA 650 (DUROS® continuous subcutaneous delivery of exenatide) for the treatment of type 2 diabetes at the 46th Annual Meeting of the European Association for the Study of Diabetes in Stockholm, Sweden.

Results of the Phase II study demonstrated substantial reductions in HbA1c and body weight during the 24 weeks of treatment with ITCA 650 at all doses. A starting ITCA 650 dose of 20 µg/day for weeks 1–12 provided effective glycemic control with the best tolerability profile. A transition to ITCA 650 at 60 µg/day for weeks 13–24 was well tolerated and provided substantial incremental reductions in both HbA1c and body weight at week 24. An ITCA 650 treatment regimen involving a 20 µg/day starting dose with a transition to 60 µg/day after week 12 has been selected for a Phase III clinical trial, which is anticipated to begin enrollment in early 2011.

"We are very encouraged by the results observed in this study and the high level of enthusiasm expressed by patients and investigators," said Kurt Graves, executive chair of the board for Intarcia. "ITCA 650 is a novel therapeutic approach for type 2 diabetes that holds new promise for many patients and physicians who want highly effective glucose reductions and weight loss without the tradeoff associated with having to start potentially lifelong and frequent self-injections." Graves added, "ITCA 650 also holds the promise to ensure patient compliance and long-term control given the breakthrough nature of its continuous delivery with just one or two placements per year."

China Pharma Holdings, Inc. Successfully Completes Phase I Clinical Trials of New Anti-drug-resistance Antibiotic

PRNewswire-Asia-FirstCall: September 22, 2010 – HAIKOU CITY, CHINA – China Pharma Holdings, Inc. (NYSE Amex: CPHI), which develops, manufactures, and markets specialty pharmaceutical products in China, announced that the company has successfully completed Phase I clinical trials of its novel cephalosporin-based combination antibiotic.

Cephalosporin continues to be the most widely prescribed class of antibiotics in China. According to the SFDA, approx. 50% of antibiotic sales are derived from cephalosporin. Sales of cephalosporin antibiotics were estimated to be over $6 billion in 2009 and are projected to be $7.5 billion in 2010, $11 billion in 2012, and $17.4 billion in 2015. Due to broad usage of antibiotics, including cephalosporin, drug resistance has become a significant issue in China. The company believes its new combination antibiotic possesses substantial competitive advantages in this environment and believes the market opportunity for this drug can reach $50 million within three years of product launch. The SFDA has designated the company's combination antibiotic as a class 1 drug, which carries five-year exclusivity when approved.

The company's anti-drug-resistance antibiotic, which combines a third-generation cephalosporin and a β-lactamase inhibitor, is expected to be indicated for a wide variety of infections throughout the body, including upper and lower respiratory tract infections (especially for pneumonia and bronchitis), ear and nose infections, bacterial septicemia, meningitis, skin and skin structure infections, bone and joint infections, abdominal infections (peritonitis, cholecystitis, etc.), upper and lower urinary tract infections, gonorrhea, and genital infections.

Greater prevalence of drug-resistant extended-spectrum β-lactamase (ESBL) producing bacteria, such as the Enterobacteriaceae family, has prompted numerous *in vivo* and *in vitro* studies of the efficacy of this combination. The combination has demonstrated 94.6% efficacy against bacteria strains resistant to the cephalosporin component alone. Beyond this clear benefit, the combination exhibits a greater spectrum of activity against microorganisms like anaerobic bacteria and pseudomonas, which are not susceptible to the cephalosporin component alone.

Phase I of the clinical trials focused on the study of clinical pharmacology, as well as evaluation of safety in the human body, through observing tolerance and pharmacokinetics to provide support for dosage and drug delivery design. Subjects enrolled in the company's Phase I clinical trials were administered medicine in dosages that varied depending on their assigned subject groups. The drug tolerance trials included both single tolerance trials and multiple tolerance trials.

"We are very pleased to announce the successful completion of Phase I clinical trials of our new drug candidate with excellent

results," commented China Pharma CEO and President Zhilin Li. "Our novel combination drug addresses growing resistance to cephalosporin. One of the two primary ingredients in our combination product has been placed on the government's essential drug list, boosting its overall usage in basic level hospitals, which may exacerbate resistance issues in the coming few years and provide an even greater opportunity for China Pharma. Both ingredients in our compound already have demonstrated their efficacy in stand-alone form, so we are very optimistic about continued success in the clinical trials setting. We believe that our anti-drug-resistance antibiotic will provide a better therapeutic solution for hospitals, and will generate positive excitement among physicians and hospital professionals upon launch, especially given the limited number of new antibiotic compounds and new combination antibiotics coming to market."

FDA Accepts Aricept® Patch (Donepezil Transdermal System) NDA for Review

PRNewswire: September 17, 2010 – SAN JOSE, CA – Teikoku Pharma USA, Inc., an international specialty pharmaceutical company, announced that the U.S. Food and Drug Administration (FDA) has accepted for review the new drug application (NDA) for a new weekly transdermal patch of Aricept®, a leading medication for the treatment of Alzheimer's disease.

The company developed the weekly Aricept® patch based on a license agreement executed between Teikoku Pharma USA, Inc. and Eisai Co., Ltd. (Eisai) in February 2009. The acceptance of the NDA indicates that the FDA deems the company's submission to be sufficient to review. The NDA was submitted to the FDA by Teikoku Pharma USA, Inc. on June 30, 2010. If approved, Eisai's subsidiary, Eisai Inc., will hold marketing rights in the United States.

The Aricept® transdermal patch formulation employs a unique drug delivery system, making it the world's first weekly transdermal patch for the treatment of Alzheimer's disease. It was developed to provide a potential new treatment option for Alzheimer's disease patients who have trouble swallowing, as well as to reduce the burden on caregivers and family members who administer medication to patients.

CID to Update Interventional Cardiologists on Their Drug-eluting Stent Program

PRNewswire: September 16 – WASHINGTON, DC – CID s.r.l., a European company leader in interventional medicine, updated interventional cardiologists on the status of their revolutionary drug-eluting stent technology during The Drug Eluting Stent (DES) Summit at TCT 2010. The lecture, "Status of the CID Cre8 Polymer-free DES Program," was delivered by Alexandre Abizaid, M.D., Ph.D., chief of intervention at Instituto Dante Pazzanese, in Sao Paulo, Brazil.

Some of the highlights of the presentation included an exploration of the clinical benefits of CID's abluminal reservoir technology (ART) and drug delivery technology. By surrounding molecules of drug with amphiphilic carriers and embedding them into reservoirs on the stent's outer surface, CID drug-eluting stents are able to deliver drug to the coronary arteries without using any polymers, which can cause serious complications in patients.

CID's unique ART system, with its amphiphilic carrier, is more physiological, and patients who receive these stents are less likely to have inflammation and thrombosis within their coronary arteries. Moreover, CID DES technology features an integral bio-inducer surface (BIS), which implies less medication to prevent blood clotting after the stent has been deployed for enhanced safety.

Commenting on the innovative technology in its new Cre8 DES, Franco Vallana, chief executive officer of CID s.r.l., said, "We have always known that the more the stent and the drug delivery system are designed and developed to harmonize with the human body, the better the short- and long-term results will be. Combining ART with our innovative drug formulation with amphiphilic carrier into a completely polymer-free stent will allow doctors to provide their patients with stents that are more physiological and complement the body's natural systems."

NanoPass Technologies Ltd. and Elcam Medical Enter into a Strategic Partnership

PRNewswire: September 14, 2010 – REHOVOT and KIBBUTZ BAR'AM, ISRAEL – NanoPass Technologies Ltd., a privately held company that develops novel microneedle solutions for painless delivery of drugs and vaccines, recently secured a strategic investment and manufacturing agreement with a leading medical device manufacturer, Elcam Medical. Existing investors, including Ofer Hi Tech and D Partners, also participated in the round.

As part of the investment, Elcam CEO Ehud Raivitz and Ilan Neugarten of D Partners will join NanoPass's Board of Directors. Raivitz remarked, "We are happy to enter into this partnership with NanoPass. I have been impressed by their innovative technology, positive clinical data and achievements. I look forward to leveraging Elcam's capabilities in production and engineering for the mutual benefit of both companies. The collaboration with NanoPass will enable Elcam to provide its customers with access to the most advanced intradermal delivery technology that can address their needs in various applications."

Dr. Yotam Levin, chief executive officer of NanoPass, commented, "We are excited to enter into this strategic partnership with Elcam, a long-time supplier of disposable medical products for the medical and pharma industries. We see a significant synergy between our companies. Along with the regulatory approvals we have recently obtained from the FDA and other regulatory bodies, securing a reliable and highly experienced manufacturer is a key component towards full commercialization of our products. The investment will allow

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NanoPass to develop additional pharmaceutical clients and prepare for market launch."

NanoPass Technologies was founded by Dr. Shuki Yeshurun under the auspices of the Naiot Technological Incubator. The company is backed by prominent Israeli and U.S. investors, including Ofer Hi Tech, D Partners, WFD Ventures, and Elcam Medical. Elcam Medical (Bar'Am, Israel) is a leading worldwide OEM supplier, servicing the medical industry, specializing in the areas of fluid management, vital signs monitoring, and drug delivery.

MicronJet is a microneedle-based device for ID delivery of vaccines and drugs. The device allows for consistent, reliable, and simple delivery of drugs directly into the skin. MicronJet has proven efficacy and safety in multiple applications, including seasonal flu vaccines, insulin, and lidocaine. MicronJet is approved for marketing in various leading territories.

NanoPass recently concluded the world's first intradermal h1n1 pandemic flu vaccine study, demonstrating equivalent immunogenicity to intramuscular delivery using 20% of the dose. In other clinical trials conducted by NanoPass and third parties, it has been shown that injecting a seasonal influenza vaccine directly into the skin allows for the reduction of the dose required for the same immune response (dose sparing). Further, using an equivalent dose may actually increase a vaccine's immunogenicity.

Purac to Build New Plant for Biomedical Resorbable Polymers in the United States

September 10, 2010 – GORINCHEM, NETHERLANDS – Purac has announced its investment in a new manufacturing facility for its biomedical polymers. The plant is meant to support the growing resorbable polymers business of Purac Biomaterials. Purac currently operates a plant for biomedical polymers in the Netherlands. This second facility will be built in the United States. The investment for this new plant will be €15 million. The construction of the facility will start in 2011 and is expected to be completed before the end of the year.

Arno van de Ven, Purac vice president chemicals and pharma, commented, "This represents an important step in the biomedical polymer business and shows Purac's continued commitment to this market. It provides us with the capability to support the growth of our existing and new business partners." In addition to an increase in production capacity, the new facility will bring Purac Biomaterials more flexibility and a more balanced presence in its global markets.

Menno Lammers, director of Purac Biomaterials, stated, "As an experienced supplier to pharmaceutical and medical device companies, we understand the importance of guaranteed supply continuity. Over the last years, the importance of risk management has increased and with this facility we will be in the unique position to provide our customers with dual sourcing."

The Purac Biomaterials business comprises lactide-based polymers such as poly lactic acid (PLA) and lactide/glycolide copolymers (PGLA). The technology as developed for Purac's biomedical polymers also formed the basis for Purac's activities in L- and D-lactides for bioplastics such as PLA.

Purac is a leading company in food preservation, green chemicals, and lactic acid-based bioplastics and the worldwide market leader in lactic acid, lactic acid derivatives, and lactides. Purac has more than 75 years of experience in the development, manufacturing, and marketing of these products in a broad range of industries. Purac operates production plants in the United States, the Netherlands, Spain, Brazil, and Thailand and markets its products through a worldwide network of sales offices and distributors. Purac is headquartered in the Netherlands and is a part of CSM.

Bacterin International Holdings, Inc. to Launch Dermal Scaffold Product Line Called hMatrix™

PRNewswire: September 8, 2010 – BELGRADE, MT – Bacterin International Holdings, Inc. (OTC Bulletin Board: BIHI), a developer of anti-infective coatings for medical applications and processor of revolutionary tissue graft material, has launched a new product line, hMatrix™, a dermal scaffold used in wound repair. The hMatrix™ dermal scaffold is an extension of Bacterin's core biologics technology and the company's third human acellular biological scaffold. The company is planning commercial release of hMatrix™ during the first quarter of 2011.

Bacterin's core technology designs and processes human acellular biological scaffolds that can incorporate the patient's own stem cells or bioactive agents for accelerated regeneration of tissue. To date the company has focused on bone, subchondral bone repair, and now has extended its technology to address dermal healing and repair. Bacterin's hMatrix™ is an acellular matrix made from donated human dermal tissue that is used to replace a patient's damaged tissue. hMatrix™ provides a natural collagen tissue scaffold that promotes cellular ingrowth and tissue vascularization and regeneration. The hMatrix™ scaffold tissue reabsorbs into the patient's dermal tissue for a biocompatible, natural repair.

The company initially intends to focus the new dermal product line on three indications: diabetic ulcers/wound repair, hernia repair, and breast reconstruction – (an estimated market of approx. $2.5 billion annually) but plans to broaden its focus into other non-homologous uses, such as rotator cuff and tendon augmentation as it receives FDA approval for these additional indications. Approximately half of the dermal repair market today utilizes allografts, which are used in primary repair for larger, more complicated defects. Given the high barriers to entry into the market, suppliers of dermal allografts are relatively few. Bacterin's new entrance in the dermal allograft market provides a highly biocompatible scaffold that can support a patient's own stem cells or bioactive agents.

"As an organization focused on responding to customer needs, our new dermal graft is addressing a supplemental product request by a number of surgeons currently using our Osteo product line. The extension of our proprietary core technology to dermal scaffolds is a natural progression of our existing capabilities, and a convenient leveraging of our operations and sales network," commented Guy Cook, Bacterin president and CEO. "Our skilled technicians already facilitate the preservation of donor tissue in our five Class 100 clean rooms, processing bone and subchondral bone grafts. With the addition of several technicians, we are able to add the processing of a dermal scaffold within our current manufacturing protocol. We plan to source the new dermal scaffold product line from the same donors used to generate Bacterin's bone and subchondral bone scaffold product lines, creating further processing synergies. In addition, the dermal scaffold will be marketed and distributed through our current sales force and independent distribution partners."

Generex Signs Marketing and Distribution Deal for Glucose RapidSpray™ with Merck and Will Market the Product as Diabion® GlucoShot®

PRNewswire: September 7, 2010 – WORCESTER, MA – Generex Biotechnology Corporation (Nasdaq: GNBT), the leader in drug delivery for metabolic diseases through the inner lining of the mouth, has entered into a long-term marketing and distribution agreement with Merck, S.A. de C.V. in Mexico for the distribution of one of the company's proprietary over-the-counter products, glucose RapidSpray™ brand formulated glucose spray product. Merck will market and distribute the product in Mexico as Diabion® GlucoShot®.

Merck was founded in Mexico in 1930 as one of the first pharmaceutical producers. Today, Merck, S.A. de C.V. manufactures and sells a great variety of products for the treatment of pain, diabetes, thyroid problems, colds, growth hormone, multiple sclerosis, and cancer, among other illnesses.

Glucose RapidSpray™ (www.GlucoseRapidSpray.com) is a proprietary, innovative alternative for people who require or want additional glucose. Glucose RapidSpray™ delivers a fat-free, low-calorie glucose formulation that was developed using the company's proprietary buccal drug delivery technologies. Glucose RapidSpray™ delivers glucose directly into the mouth, where it is absorbed. It is simple to carry and use, with no large tablets to chew or messy gels to swallow. Presently, Glucose RapidSpray™ is available in retail pharmacies across Canada, the United States, and in independent stores and pharmacies in the Middle East. The processes for registering the product for retail marketing in other countries are underway.

"We are so pleased to enter the expansive Mexican marketplace through this marketing agreement with Merck in Mexico," said Bill Abajian, senior executive advisor to Generex, global licensing and business development. "We believe that Glucose RapidSpray™ will become a staple within consumer households as more people become familiar with the benefits of the product. We expect that with the marketing expertise that Merck Serono provides penetration within the Mexican marketplace will open up additional markets for the company's product in Latin and South America as well as the other global markets within which a foothold has already been made."

"We welcome Generex, to proudly contribute to the growth of our diabetes franchise with a world-class technology for our Consumer Health Division with a comprehensive product offering and innovative power," said Dr. Arturro Torres y Gutierrez Rubio, medical director for Merck in Mexico. "We will now move quickly to bring together the expertise and complementary capabilities of both Merck and Generex to capture the significant opportunities in the high growth of the market."

Bend Research Expands Pharmaceutical Manufacturing Capabilities

PRNewswire: September 7, 2010 – BEND, OR – Bend Research Inc. (www.bendres.com), a leading independent drug-formulation development and manufacturing company, has announced that it is expanding its pharmaceutical manufacturing capabilities for hot-melt extrusion. The company has purchased intermediate-scale equipment for hot-melt extrusion at its contract manufacturing facility to provide additional processing options for its clients.

The new equipment—an 18-mm extruder—provides capacity between existing 7.5- and 27-mm extruders. This enables manufacture at the appropriate scale for the development phase of the compound. The equipment reduces the amount of drug required for development work, resulting in savings to Bend Research clients and enables rapid, efficient advancement of compounds. The three extruders enable seamless scale-up of a formulation from small-scale development work through large-scale manufacture of clinical supplies using cGMP regulations for human clinical trials.

"This added capability strengthens our established position as a leading drug-formulation outsource for pharmaceutical companies that need innovative delivery technologies," said Bend Research President and CEO Rod Ray. "In addition, the new equipment broadens the company's technology offerings for the delivery of low-solubility drugs."

Bend Research is a recognized international leader in the pharmaceutical industry for technologies that improve the solubility and bioavailability of hard-to-deliver pharmaceutical compounds. The company is well-known for its spray-dried dispersion (SDD) technologies, which have been used to advance hundreds of low-solubility compounds.

Based on pharmaceutical industry estimates, as many as 40% of pharmaceutical compounds in development require solubilization technologies to be orally absorbed into the body. The SDD and hot-melt extrusion technologies are well-known for their abilities to improve oral absorption.

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Ray said Bend Research has had the capability to manufacture hot-melt extrusions since 2002 at its cGMP manufacturing facilities. Bend Research is adding specialized suites for high-potency pharmaceutical compounds and has a full range of equipment (e.g., mills, blenders, tableting equipment) to transform the hot-melt extrusion formulations into suitable dosage forms.

"Many people don't realize that the first commercial pharmaceutical product we helped bring to market was based on hot-melt extrusion technology," Ray noted. "We worked closely with a client to develop an innovative modified-release product based on hot-melt extrusion that made it possible for patients to take a single dose of an antibiotic rather than a multi-day regimen. As an established leader in hot-melt extrusion formulation and processing, we look forward to helping even more clients with this added capability."

For more information about Bend Research and its formulation and manufacturing capabilities, please contact Dana Settell at Dana.Settell@bendres.com or +1.541.382.4100.

Custom-made Gels Suitable for Drug Delivery

Wageningen University: September 7, 2010 – WAGENINGEN, THE NETHERLANDS – That gels based on proteins from yeasts can be used as drug delivery systems and carriers of antibodies is the most important conclusion from Helena Teles' doctoral research at Wageningen UR Food & Biobased Research. The custom-made proteins from the yeast *Pichia pastoris* are an alternative for animal gelatins and collagens used in the medical and pharmaceutical industries.

Teles' research shows that when other proteins are enclosed in the gel, they slowly leak out. Moreover, it turns out that erosion causes the gel to slowly dissolve from the exterior to the interior. In this way, all proteins enclosed in the gel are slowly passed on to the environment. These characteristics make the gels, which are derived from yeasts, suitable for drug delivery.

Researchers Frits de Wolf and Marc Werten from Food & Biobased Research designed these protein molecules, which collectively form a network and swell in water. Each molecule consists of two small end pieces and a large middle piece, all of which can be custom designed. The molecule's short ends bond with other molecules to form a network. The resulting gel can enclose other molecules, such as medicines or antibodies, and proteins that are used by the human body to eliminate viruses and bacteria. Pieces of protein can also be built into the gel molecules themselves.

By letting the yeasts produce shorter or longer molecules, the melting temperature or rigidity of the gel, for example, changes, and this can cause slower or faster delivery. Senior researcher De Wolf explained, "Because we can adjust their properties, these gels from biomaterial are also very suitable for other applications, for example, to cover a wound, to reinforce connective tissue or to seal off blood vessels during an operation."

These gels can offer an alternative to animal-based gels and possibly to the synthetic polymers that are currently being used in the pharmaceutical and medical industries. These industries are looking for animal-free alternatives for gelatin and collagen because of the virus and prion contamination risks that animal-based gelatins and collagens bring with them.

Helena Teles' research at Wageningen UR Food & Biobased Research is partially financed within the B-Basic Programme and has been realized in collaboration with Utrecht University and the Laboratory of Physical Chemistry and Colloid Science at Wageningen University.

Archimedes Pharma Receives European Marketing Authorization for PecFent for the Treatment of Breakthrough Cancer Pain

PRNewswire: September 1, 2010 – READING, ENGLAND – Archimedes Pharma Ltd., a leading international specialty pharma company, has announced that the European Commission has granted marketing authorization for its lead product, PecFent, an innovative fentanyl nasal spray for the treatment of breakthrough cancer pain (BTCP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain.

Breakthrough cancer pain is a sudden, unpredictable episode of pain that is severe to excruciating in intensity; it affects 24–95% (avg. 62%) of all cancer patients despite background pain medication. Episodes can often reach maximum intensity in 5 min, typically lasting 30–60 min. Most people who have breakthrough cancer pain experience several episodes a day.

PecFent contains fentanyl, a highly potent opioid analgesic, and uses an Archimedes Pharma nasal drug delivery system (PecSys) to deliver fentanyl in a rapid but controlled manner designed to match the time course of the typical breakthrough pain episode. In two randomized, well-controlled, double-blind, Phase III clinical trials, PecFent demonstrated onset of pain relief as early as 5 min, as well as clinically meaningful pain relief within 10 min.

Jeffrey H. Buchalter, president and chief executive officer of Archimedes Pharma, commented, "The grant of European marketing authorisation for PecFent provides a new therapy to improve the treatment options for adult patients with breakthrough cancer pain. This is also a transformative milestone for Archimedes Pharma as we have established commercial operations in Europe and look forward to launching PecFent in major European markets in the coming months."

Prof. Marie Fallon, St. Columba's Hospice Chair of Palliative Medicine, University of Edinburgh, Edinburgh Cancer Research Centre (CRUK) Western General Hospital, Edinburgh, commented, "The availability of this significant innovation is very important. Being a nasal spray, its ease of use allows patients to treat their breakthrough cancer pain episodes conveniently, wherever they are, and its unique delivery system provides fast onset of pain relief meaning they can manage these episodes effectively. This is absolutely crucial for cancer patients and

PecFent offers real hope for an improvement in their quality of life."

The marketing authorization is based on the largest ever clinical development program in breakthrough cancer pain, which involved three Phase III studies, including an active comparator study and a large long-term safety and acceptability study. The program included more than 650 patients and more than 100 investigational sites in the United States, United Kingdom, Germany, France, Spain, and Italy and in a total of 13 countries across 4 continents.

Archimedes Pharma submitted a new drug application (NDA) for the product to the U.S. Food and Drug Administration (FDA) in August 2009 and is in the process of establishing a U.S. commercial organization to market the drug in the United States once approved. (Note, PecFent was previously known as NasalFent.)

Celator Pharmaceuticals Raises $20 Million in Series D Financing

PRNewswire: September 1, 2010 – PRINCETON, NJ – Celator Pharmaceuticals, a privately held pharmaceutical company developing new and more effective therapies to treat cancer based on the company's proprietary technology, has raised $20 million in a series D private equity financing. Proceeds will support completion of ongoing clinical trials and activities related to advancing the company's lead investigational product, CPX-351 (Cytarabine:Daunorubicin) liposome injection as a treatment for acute myeloid leukemia (AML). The round was led by a new investor, Thomas, McNerney & Partners, with participation by current investors Domain Associates, Ventures West Capital, Quaker BioVentures, TL Ventures, GrowthWorks Capital, and BDC Venture Capital.

"We are extremely pleased to attract a new investor of this caliber along with the continued support of our existing investors," said Scott Jackson, chief executive officer, Celator Pharmaceuticals. "This financing is an endorsement of the team, products, and technology of the company. Earlier this year we announced that CPX-351 achieved a statistically significant improvement in complete remissions in newly diagnosed, elderly AML patients compared to the standard of care in a randomized Phase 2 study. We look forward to disclosing these results and other data later this year."

In addition to Celator's clinical stage product pipeline that includes CPX-351 and CPX-1 (Irinotecan:Floxuridine) liposome injection, the company has research collaborations with Cephalon and the National Cancer Institute's Nanotechnology Characterization Laboratory.

Joining Celator's Board of Directors is Alex Zisson, partner in Thomas, McNerney & Partners. "It's rare to get the opportunity to invest in a cancer company that has already beaten the gold standard head-to-head in a first-line setting. We're excited to join Celator now as it advances an important new treatment option for patients suffering from AML," said Zisson. ■

Controlled Release Society
3340 Pilot Knob Road
St. Paul, MN 55121
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Calendar of Events

2011

46th Annual Arden Conference: Pharmaceutical Development of Biologics
March 6-11
The Thayer Hotel
West Point, NY, U.S.A.
www.aapspharmaceutica.com/meetings/workshops/Arden46/

14th Industrial Symposium and 5th Trade Fair on Microencapsulation (organized by CRS, SwRI, and Bioencapsulation Research Group)
March 7-9
The Sheraton Gunter Hotel
San Antonio, TX, U.S.A.
http://impascience.eu/bioencapsulation/2011_San_Antonio

2011 Society for Biomaterials Annual Meeting
April 13-16
Orlando, FL, U.S.A.
www.biomaterials.org

2011 AAPS National Biotechnology Conference
May 16-19
Hilton San Francisco Union Square
San Francisco, CA, U.S.A.
www.aapspharmaceutica.com/NationalBiotech

38th Annual Meeting & Exposition of the Controlled Release Society
July 30-August 3
Gaylord National Resort and Convention Center
National Harbor, MD, U.S.A.
www.controlledreleasesociety.org/main/meetings

71st FIP World Congress of Pharmacy and Pharmaceutical Sciences
September 2-8
Hyderabad, India
www.fip.org/congresses

2012

9th World Biomaterials Congress
June 1-5
New International Exhibition & Convention Center
Chengdu, China
www.wbc2012.com

39th Annual Meeting & Exposition of the Controlled Release Society
July 14-18
Centre des Congrès de Québec
Québec City, Canada
www.controlledreleasesociety.org/main/meetings