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Newsletter

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From the Editor

Arlene McDowell
New Zealand's National School of Pharmacy, Univerity of Otago
Dunedin, New Zealand

Welcome to the first issue of the *CRS Newsletter* for the new decade. We wish you a very happy new year! And, to represent the international nature of our Society—*gung hay fat choy*, *jour des étrennes*, *gutes nue Jahr*, *say hay boke-mahn he pah du say oh*, and *godt nytår*. I have fond memories of my family and the new year tradition of "first-footing." This is a European tradition, where to bring good luck a male with dark hair must be the first person to enter the house, preferably with a piece of coal, saying, "Lang may your lum reek" ("Long may your chimney smoke"). My father had dark hair, and so he was a popular visitor on new year's day. There are many lovely traditions around the world surrounding the new year, and a great CRS tradition is the annual meeting. Our CRS Annual Meeting & Exposition in 2010 will be held in Portland, OR—"The city of roses." This will help some of you solve the little mystery of why all those people had red roses on their name badges at the 2009 CRS Annual Meeting. The meeting organising committee thanks those who have agreed to be abstract reviewers for the CRS Annual Meeting in Portland. Abstract reviewing is a very important part of the meeting, and we appreciate the time and effort that goes into ensuring that the high standard of podium and poster presentations is maintained.

The *CRS Newsletter* continues to grow and provide increased communication with our members. With six issues planned for 2010, there is lots of great reading to come. As always, we welcome your contributions. Please contact a member of the *CRS Newsletter* Editorial Board if you would like to submit an article or have any suggestions about the *Newsletter*. We are also giving members the opportunity to promote images of their controlled release science on the cover of the *CRS Newsletter*. If you have a great image you would like to share, we would love to see it. Send electronic copies through the online dropbox at http://dropbox.yousendit.com/scisoc (see page 15 in this issue for more details).

In this issue you can read about the activities of a number of CRS Chapters worldwide, including a new Student Chapter at The Hebrew University of Jerusalem and be at the right place at the right time for the UKI CRS symposium in April, where you will find out about controlled release in drug delivery. I encourage you to seek out a Chapter located near you and get involved. Plus check out our regular forums, including Scientifically Speaking, Patent Watch, From the Vet Group, and In the News.

On behalf of the editorial team of the *CRS Newsletter*, I wish you a happy, healthy, and successful 2010.

Best wishes,

Arlene McDowell ■

Diane J. Burgess, Ph.D.
Board of Trustees Distinguished Professor
School of Pharmacy, University of Connecticut, Storrs, CT, U.S.A.

I'll be honest. I've been sitting at my computer for a solid half-hour now trying to write the introduction to my president's column on CRS finances. Don't worry, we're not on the brink of financial collapse. On the contrary, we are weathering the current global economic crisis.

But we haven't been untouched. And, that's what I need to talk to you about.

From a scientific, social networking, and professional development perspective, the annual meeting in Copenhagen was a complete success. The roundtable discussions, symposia, plenary sessions, speakers, and overall programming couldn't have been stronger. Unfortunately, as a result of the economic climate, far fewer of our colleagues had the opportunity and resources to attend the meeting than had been anticipated in 2006 when we first began planning this annual meeting—long before there were so many black clouds on the economic horizon. The same held true for exhibitors, who also attended in markedly fewer numbers than in previous years.

As a result, once it was over and all the numbers were in, the 2009 CRS Annual Meeting had the unlucky distinction of being registered as a CRS expense rather than the star asset it has traditionally been—an asset that has historically more than carried its weight financially. The bottom line is that the meeting resulted in a financial loss due to decreased attendance and higher venue costs—a loss that in previous years would have easily been offset, at least partially, by other revenue-generating products and services. But, those products and services have also been down this past year due to the "great recession."

So you are probably wondering: How significant is the loss, and how will it impact CRS?

While no organization (or person for that matter) ever wants to take a financial hit, especially when (as is the case with CRS) careful and conservative fiscal management have historically resulted in positive rather than negative outcomes, the most important thing I want you to know is that we can and will absorb the loss without traumatic and long-term setbacks in terms of our goals and mission. But, it does put a damper on some of the new initiatives we were considering for this year and next. Until we regain some of the losses, things will have to remain status quo for a time.

From my perspective and that of the Board of Directors, this set of circumstances may not be entirely unwelcome. As we see it, it gives us more time to reevaluate our plans, to slow down, to plot our strategy carefully against a new economic world order, and to weigh what we think we want as an organization, against what we truly need to keep our science and our Society strong. We see this as a speed bump on the road to creating a Society that is built for the long term—a Society that is solid, yet flexible enough to correct its trajectory with the sudden twists, turns, and miscalculations that will come with life in the 21st century and beyond.

Fortunately, unlike many other organizations, this economic downturn will not even come close to breaking us. We may have a few nicks and scratches before it's all done, but they won't be anything that won't heal in time. And, time is something we are wealthy enough to have plenty of.

Diane J. Burgess
crspresident@scisoc.org ■

Starting Thoughts from the C&DP Representative to the *CRS Newsletter* Editorial Board

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

Charles Frey

Greetings fellow CRS members! As I volunteer to represent Consumer and Diversified Product (C&DP) interests within the *CRS Newsletter*, I would like to first extend a sincere thank you to Jamileh Lakkis, who has done an excellent job in this role for many years. Her dedicated work has been an integral element in both bringing a more complete picture of the scope of the CRS to the *Newsletter* and enlightening everyone on the many aspects of controlled release in the C&DP areas. I also extend a thank you to Raja Sivalenka who has assisted Jamileh over the past year.

I have been a member of the CRS for approximately 10 years and became active in the C&DP track after the 2004 CRS Annual Meeting in Hawaii. It has been a fulfilling experience to work with the C&DP Committee and help promote the many interests embodied in the group. I highly value the many friendships and acquaintances that I have developed through this work and look to continue my contributions to the group.

C&DP is the net that catches the myriad controlled release applications that do not fall in the pharmaceutical or veterinary realms. The lines are often blurred between these three tracks or interests within CRS, and there are efforts within the CRS to avoid compartmentalizing them. This is a sound philosophy. Although various controlled release technologies may not be used universally across the many diverse industries represented in the CRS, the ideas and findings must be shared freely across such industry lines. Sharing is a key to innovation. Failure to share promotes compartmentalization of technologies and slows innovation.

Regardless of this underlying need to share ideas and findings, there is perhaps an equally great or greater need to ensure that the full scope of controlled release is visible in the Society. Pharmaceutical interests are significantly represented in the CRS. Failure to clearly differentiate and represent the currently smaller C&DP and veterinary interests from pharmaceutical interests reduces the visibility of these smaller interests, and thus, they become hidden elements. Subsequently, CRS growth in these areas may be limited due to the failure of potential new CRS friends and members to realize that their interests are represented by the Society.

As the CRS moves forward, I am confident that it will continue on a path that represents its mission to the fullest extent. This will include the many controlled release interests contained in the C&DP net, including food, flavors, personal care, cosmetics, fragrances, nutritionals, household products, agrochemicals, pest control, and other diverse areas. As I begin the role of C&DP representative on the *CRS Newsletter* Editorial Board, I look to maintain the presence of C&DP activity in the *Newsletter* and keep readers aware of the many aspects of controlled release included in the C&DP areas.

I encourage you to get involved in CRS activities wherever the Society may touch upon your work or needs. The CRS thrives on the time, energy, and spirit invested in sharing information. Our collective energies are what make the Society. ■

Portland Awaits

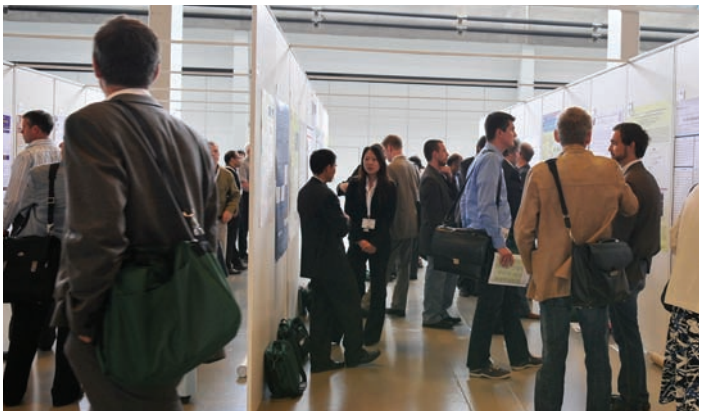
Ijeoma F. Uchegbu
Professor of Pharmaceutical Nanoscience
CRS Scientific Secretary

Ijeoma F. Uchegbu

A small crowd gathers around a poster in the aisle. Delegates stand bumper-to-bumper listening as the author explains their latest findings, punctuating the address with audible nods of understanding and the odd question. Familiar sight? Yes. A sight repeated intermittently down the crowded aisle. This is the CRS Annual Meeting; a place where science is shared and new ideas are born. Dare to miss it? I never do. CRS delegates are a friendly bunch and always a pleasure to catch up with, and this is the only meeting where completely new drug delivery science is unveiled year after year after year.

Last year you declared in our survey that 94% of the science on display at the CRS was either excellent, very good, or good. A hard act to follow, but we have tried to do just that. The science will be great. "Personalised Medicines and Products for the Next Generation" promises to give you the very latest in genomics, stem cells (yes we can!), biomarkers, translational medicine, theranostics, and much more, plus all your favourites—hydrogels, transdermal delivery, and protein delivery. This year we have a special Roche-sponsored session on siRNA delivery. This exciting session will give delegates an opportunity to learn about real therapeutic advances in this very important area.

Downtown—RiverPlace District. Photo courtesy of Travel Portland/ Edward Nugent.



Attendees conversing in the poster area at the 2009 CRS Annual Meeting & Exposition.

Mauro Ferrari

One area that you have consistently told us you cannot get enough of is tumour targeting. In response to this, we offer Mauro Ferrari of the University of Texas, Houston, M. D. Anderson Cancer Center, who will be a plenary speaker on Wednesday, July 14. Ferrari is an expert in nanoparticle tumour therapies. Using mathematical concepts to understand convective flow within biological matrices, Ferrari has designed modular particles that have the ability to sequentially and efficiently breach biological barriers before finally shedding their payload at their site of action within tumour cells. Ferrari's work offers a new approach to the age-old problem of tumour targeting, and his lecture is not to be missed.

Well is that all? Just science? I hear you ask. No, is the short answer. Portland is a wonderful city. With only half a million residents, this city is small, friendly, and has more people with advanced degrees compared with the average for the rest of the country (33% of those 25 years of age or older hold university degrees versus the national average of 24%). The city also prides itself on its "green" credentials and has good public transport links. Furthermore, Portland nestles within a landscape of well-known vineyards and a large number of hiking and biking trails. The quality of life is justifiably highly rated. Now, I am not suggesting that after the conference you resist the urge to go home, because I know your laboratory needs you. All I am saying is that you will be sure to get a very warm welcome and find lots of things to do between lectures, posters, and networking. Within the city there many bars, pubs, restaurants, and coffee shops—ideal places to continue that conversation you started in the poster aisle. ■

See These Exhibitors at the 37th CRS Annual Meeting & Exposition

July 10-14, 2010 • Portland, Oregon, U.S.A.

Exhibiting companies that have reserved space at the 37th Annual Meeting & Exposition of the Controlled Release Society, as of press time, are listed below. For ongoing updates, visit www.controlledreleasesociety.org/meeting/exhibitors/currentExhibitors.cfm.

3M Drug Delivery Systems
Abraxis BioScience
Adhesives Research
Alkermes, Inc.
ARmark Authentication Technologies, LLC
Asahi Kasei Chemicals Corp.
Avanti Polar Lipids
Azopharma Contract Pharmaceutical Services
Banner
BASF Corp.
Bend Research, Inc.
Bio-Images Research Ltd.
Boehringer Ingelheim Chemicals, Inc.
Buchi Labortechnik AG
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Croda, Inc.
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Phase Separation Behavior of Fusidic Acid in Microspheres Influences Morphology and Drug Release

Samuel E. Gilchrist, Kevin Letchford, Chiming Yang, and Helen M. Burt
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Bacterial infections resulting from orthopedic surgeries are typically managed by prophylactic and post-surgical treatment with systemic antibiotics. Commonly, this strategy fails to produce therapeutic tissue concentrations of the antibiotics. By direct application of antibiotics to the site of infection or potential infection, it is possible to achieve higher tissue levels for prolonged periods of time, while simultaneously avoiding systemic side effects. The primary method of local antibiotic delivery in orthopedic surgeries has been via antibiotic-loaded poly(methylmethacrylate) (PMMA) bone cement and beads; however, these systems need to be surgically removed from the implantation site and are characterized by sub-optimal antibiotic elution profiles (1). Bioresorbable drug-loaded carriers, including poly(lactic-*co*-glycolic acid) (PLGA) and poly(hydroxybutyrate-*co*-hydroxyvalerate) (PHBV) show promise for the delivery of a variety of antibiotics for the treatment of bone infections.

Fusidic acid (FA) has potential for the treatment of orthopedic infections due to its activity against organisms that commonly cause prosthetic joint infections (2). Localized and controlled delivery of FA has been proposed for the treatment and prevention of bone infections in orthopedic medicine. However, the literature is limited. There are only a few reports on the local administration of FA, which include a study of FA released from non-biodegradable PMMA bone cement (2,3), bioresorbable plaster of Paris (calcium sulfate hemihydrate) beads (4), and delivery of sodium fusidate (sodium salt of FA) from PLGA microspheres (5). Therefore, the objective of this work was to develop and characterize the solid-state properties of PLGA and PHBV microspheres for the local and controlled release of FA.

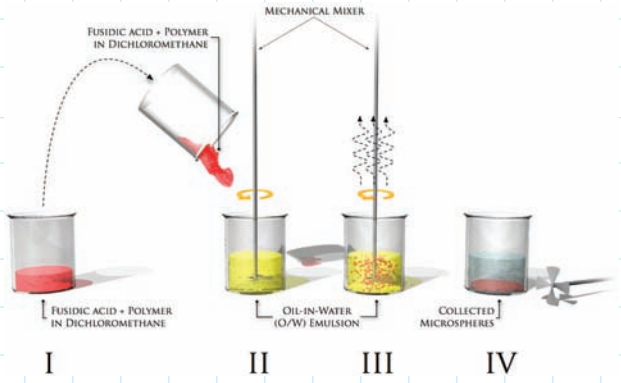

Figure 1. *Schematic representation of the O/W emulsion technique used to encapsulate FA. (I) FA and PLGA or PHBV are dissolved in DCM. (II) FA-polymer solution is added drop-wise to an excess aqueous medium containing 2.5% PVA, and stirring at 600 rpm forms the O/W emulsion. (III) Stabilization of the emulsion is achieved by constant mechanical agitation and subsequent evaporation of the organic solvent. (IV) FA-loaded microspheres are washed with distilled water and collected via centrifugation.*

FA-loaded microspheres were prepared using an oil-in-water (O/W) single-emulsion method (Figure 1). Either PLGA (50/50 or 85/15) or PHBV (5% or 12% HV) were dissolved with FA (30%, wt/wt) in dichloromethane (DCM) at 10% (wt/vol) and added drop-wise into 100 mL of a 2.5% PVA solution with stirring at 600 rpm. The dispersions were stirred for 2.5 hr to evaporate the DCM. Microspheres were collected by centrifugation at 3,000 rpm for 5 min and washed four times with distilled water.

SEM analysis of the microspheres revealed that FA-loaded PLGA microspheres had a unique morphology characterized by spherical protrusions on the surface, whereas FA-loaded PHBV microspheres had recessed spherical dimples (Figure 2A and C). After 7 days of *in vitro* release, the protrusions on the PLGA microspheres disappeared and were replaced with spherical depressions (Figure 2B). As determined by Raman spectroscopy, it was confirmed that the protrusions on the PLGA microspheres consisted of FA-rich regions surrounded by PLGA-rich regions. In contrast, the FA encapsulated in PHBV was uniformly distributed throughout the polymer matrix (Figure 3). In order to determine whether these FA-rich regions were crystalline in nature, X-ray powder diffraction (XRPD) patterns of FA-loaded microspheres were compared with that of the as-received drug and drug recrystallized from DCM. The encapsulation of FA in PLGA

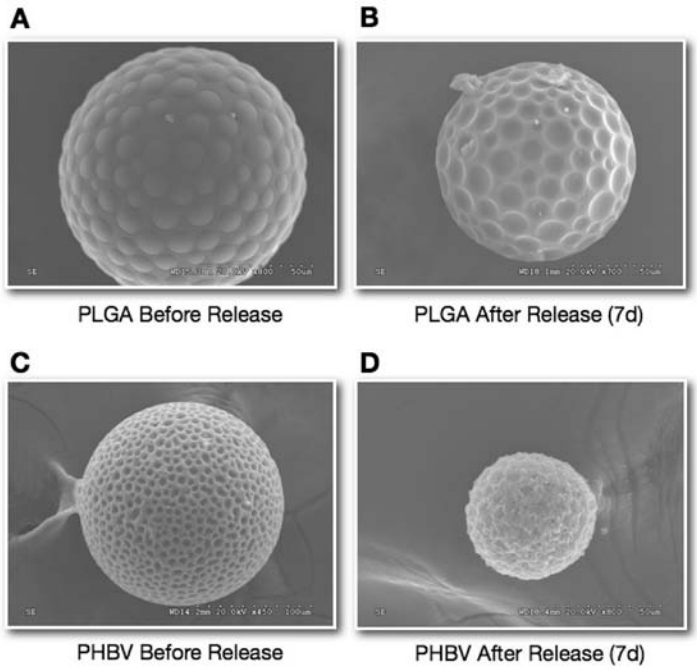

Figure 2. *Scanning electron microscopy images illustrating the changes in surface morphology of 30% (wt/wt) FA-loaded PLGA (85/15) and PHBV (12% HV) microspheres following 7 days of* in vitro *drug release in PBS.*

microspheres resulted in an amorphous XRPD halo, indicating that the protrusions lacked crystalline structure (Figure 4). Interestingly, the XRPD diffraction patterns of the as-received FA and recrystallized FA differed significantly, with major peaks at 6.67°, 12.79°, and 17.59° 2θ for the as-received drug and 10.97°, 13.55°, and 15.57° 2θ for the recrystallized drug, indicating the possibility of a previously unreported polymorphic form of FA (Figure 5). The XRPD results were confirmed by thermal analysis of FA-loaded PLGA microspheres, which were devoid of a melt endotherm due to FA. Polymorphism of FA was confirmed by thermal analysis of the as-received FA, which displayed an initial melt endotherm at 135°C followed by a recrystallization exotherm at 153°C and a final melt endotherm at 178°C. The recrystallized drug only displayed a single melt endotherm at 178°C (data not shown). Microspheres composed of PLGA were characterized by a rapid burst release of approx. 75% and approx. 30% for PLGA of composition 50/50 and 85/15, respectively, on the first day, followed by virtually no release for the remainder of the experiment. The burst release was attributed to the loss of the phase-separated regions of FA as depicted by the SEM micrographs showing loss of the protrusions after 7 days of incubation in PBS. The amount of drug released in the burst phase was correlated to the hydrophilicity of the polymer, with 50/50 PLGA displaying a larger burst release than 85/15 PLGA. In contrast, PHBV microspheres displayed a burst release followed by a slower, controlled release of FA (Figure 6). This was attributed to the dispersed nature of FA in the polymer matrix.

In this work it was found that the encapsulation of FA in PLGA microspheres results in a solid-state phase separation phenomenon, manifesting as spherical protrusions on the surface of drug-loaded microspheres. Through solid-state characterization techniques, it was determined that these protrusions were FA-rich domains that were non-crystalline in nature. During this characterization, a previously unreported polymorph of FA was discovered, which is currently under further investigation by our group. These phase-separated FA regions were attributed to the large *in vitro* burst release, the magnitude of which was determined by the hydrophilicity of the copolymer. In contrast, FA was evenly dispersed throughout PHBV, leading to a controlled release of drug over 21 days.

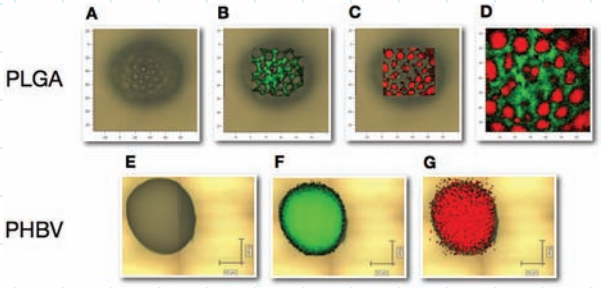

Figure 3. *Raman spectroscopy images of FA distribution in 30% (wt/wt) FA-loaded PLGA (85/15) and PHBV (12% HV) microspheres. PLGA microsphere images (top row):* ***A,*** *white light montage (50× magnification);* ***B,*** *distribution of PLGA-rich regions (green);* ***C,*** *distribution of FA-rich regions (red);* ***D,*** *combined distribution. PHBV microsphere images (bottom row):* ***E,*** *white light montage (20× magnification);* ***F,*** *distribution of PLGA-rich regions (green);* ***G,*** *distribution of FA-rich regions (red).*

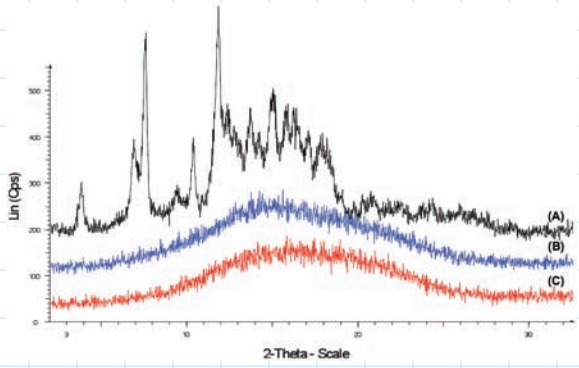

Figure 4. *X-ray powder diffraction patterns of* ***A,*** *as-received FA; 30% (wt/wt) FA-loaded PLGA (85/15) microspheres; and* ***C,*** *control (no drug) 85/15 PLGA microspheres.*

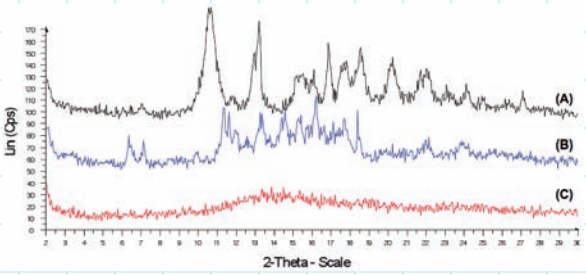

Figure 5. *X-ray powder diffraction patterns of* ***A,*** *as-received FA;* ***B,*** *FA slowly recrystallized from DCM at 4°C; and* ***C,*** *amorphous FA.*

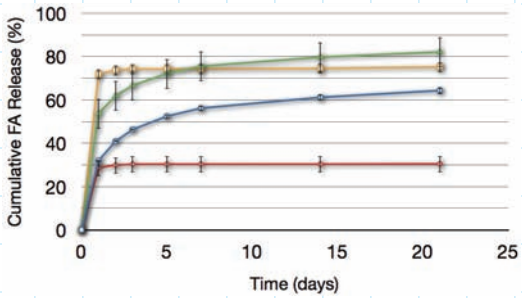

Figure 6. In vitro *FA release profiles from 30% (wt/wt) FA-loaded 50/50 PLGA (yellow line), 85/15 PLGA (red line), 5% HV PHBV (blue line), and 12% HV PHBV (green line) in PBS at 37°C.*

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Tailoring *In Vitro* Cell Responses of Porous Silicon Micro- and Nanoparticles

Hélder A. Santos,[1,2] Luis M. Bimbo,[1] Jarno Salonen,[3] Vesa-Pekka Lehto,[4] and Jouni Hirvonen[1]

Introduction

Biomedical applications of inorganic nanomaterials have been actively investigated recently (1–5), especially in areas such as imaging and drug delivery applications (3). These materials are thought to improve the efficiency of cancer therapy and to provide efficient and user-friendly administration of other active pharmaceutical ingredients. For example, many potential molecules cannot be delivered in oral form due to their poor dissolution/solubility and/or pharmacokinetic properties in the intestinal lumen, poor permeation properties in the GI tract, and high intestinal or hepatic first-pass metabolism. Porous silicon (PSi) materials have several advantages over existing materials for drug delivery (2), overcoming most of the abovementioned problems in drug delivery of poorly soluble drug molecules. They can be fabricated to be stable under the harsh conditions of the stomach and GI lumen, maintaining their physicochemical properties (2). In addition, PSi particles possessing different pore sizes in the mesoporous range (2–50 nm), along with desired surface chemistry, morphology, and high surface areas (200–700 m^2/g), enable utilization of tailored PSi particles, with optimal loading of drug molecules into the pores, resulting in, for example, improved drug release/dissolution and permeation behavior (4,5).

In addition to the beneficial functionalities of the nanomaterials, which stem from their reduced size, safety issues also need to be assessed at the cellular level before they can be implemented in human therapeutics. The aim of the present study was to evaluate *in vitro* how micro- and nano-sized PSi materials interact with human intestinal carcinoma-derived cells (Caco-2) and RAW264.7 mouse macrophage cells. For this purpose, different methods were utilized to evaluate cytotoxicity, cellular permeability, and cell association or uptake. The study was performed as a function of particle size and surface chemistry.

Results and Discussion

PSi micro- and nanoparticles, thermally hydrocarbonized-PSi (THCPSi), and thermally oxidized-PSi (TOPSi) were prepared using an anodization method (2). The THCPSi and TOPSi particles were hydrophobic and hydrophilic, respectively, and both had negative zeta-potentials. The physicochemical properties of the particles are compared in Table 1 and Figure 1.

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The TOPSi and THCPSi particles were incubated with undifferentiated Caco-2 cells for 24 hr. Their cytotoxicity was evaluated with a luminescence-based assay (Figure 2). The PSi particles of 1–25 µm decreased the cellular ATP content more than the other particles. The highest decrease was observed for

Table 1. Specific surface area (*A*), pore volume (*V*), and average pore diameter (*D*) of the THCPSi and TOPSi particles used in the present study

Particles	*A* (m^2/g)	*V* (m^3/g)	*D* (nm)
TOPSi microparticles	223	0.73	10.7
TOPSi nanoparticles	233	0.52	9.1
THCPSi microparticles	322	0.81	9.8
THCPSi nanoparticles	202	0.51	9.0

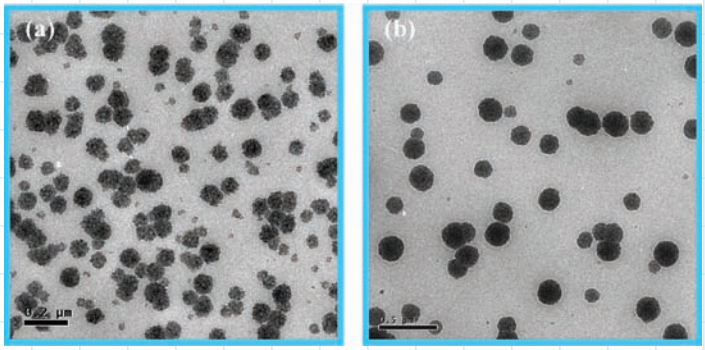

Figure 1. *TEM pictures of the PSi nanoparticles: (**a**) TOPSi (80 nm); (**b**) THCPSi (210 nm). Scale bars: (**a**) 200 nm; (**b**) 500 nm.*

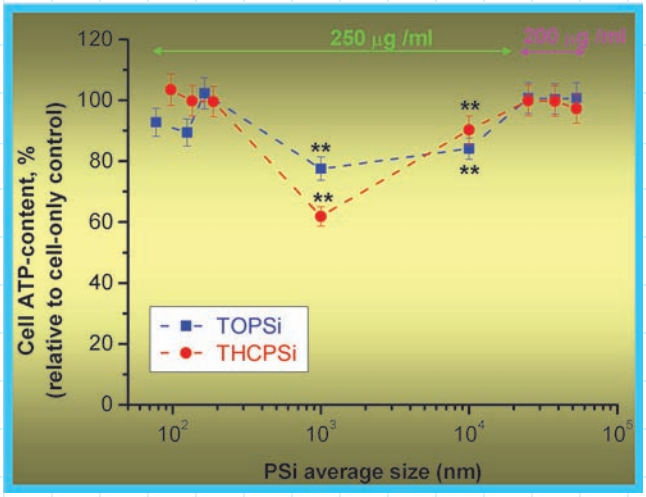

Figure 2. *ATP contents in Caco-2 cells as a function of THCPSi and TOPSi particle size. Concentrations of nano- and microparticles were 250 and 200 µg/mL, respectively. Untreated cells were used as a control. Statistical differences are denoted by ** ($P < 0.01$).*

the THCPSi particles and was attributed to their surface chemistry (hydrophobic) and ability to strongly interact with the cell membranes.

ATP depletion of the cells may indicate cellular stress induced by intracellular reactive oxygen species (ROS) production. The intracellular ROS in Caco-2 cells (Figure 3) in the presence of nanoparticles was much lower than that obtained with the positive control (H_2O_2, 100%). The TOPSi particles (<100 nm and 1–10 µm) induced more intracellular ROS production, possibly due to the cell internalization of the TOPSi particles (results not shown). No significant changes in the intracellular ROS were observed for the THCPSi particles, suggesting that these particles tend to interact more with the extracellular membrane. The results suggest different mechanisms of cell–particle interactions, which should be taken into account for intended drug delivery applications of these materials.

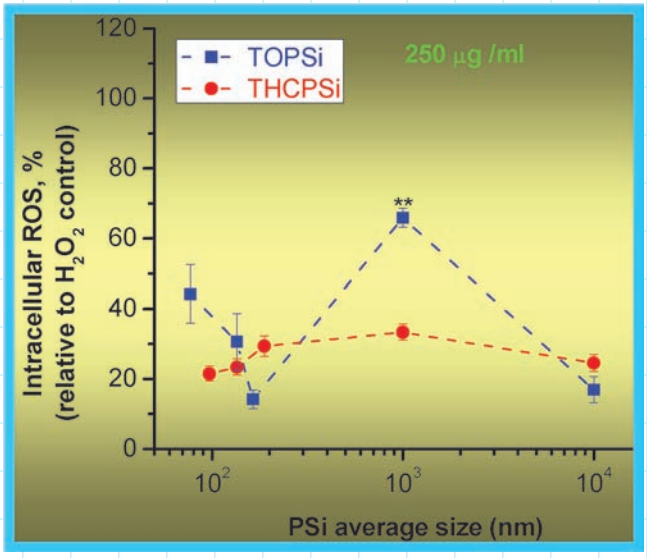

Figure 3. *Intracellular ROS were detected using dichlorodihydrofluorescein diacetate staining after the incubation of undifferentiated Caco-2 cells with TOPSi and THCPSi particles (*c = *250 µg/mL) for 24 hr at 37°C. All the results plotted were statistically different from treated cells with 0.09% H_2O_2 (ROS 100%) (*P < *0.01). Statistical differences to untreated cells are denoted by ** (*P < *0.01).*

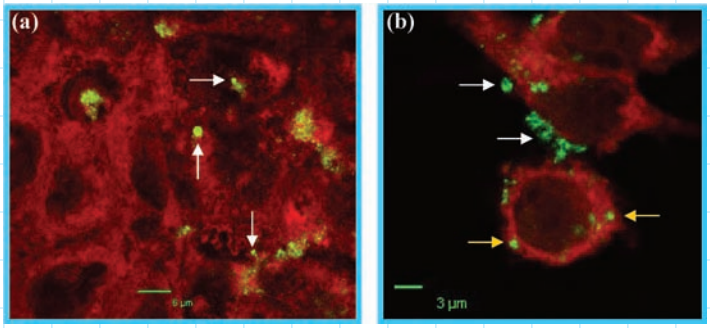

Figure 4. *Confocal z-stacks microscopy images of differentiated Caco-2 monolayers (**a**) and RAW264.7 macrophage (**b**) in the presence of fluorescently labeled 170-nm THCPSi nanoparticles,* c = *100 µg/mL (**a**) and 15 µg/mL (**b**). The images are overlays of transmitted and fluorescence images.*

Cellular association and cell uptake of fluorescently labeled THCPSi nanoparticles were studied with confocal-laser scanning microscopy. These nanoparticles did not permeate significantly in or across the Caco-2 monolayers over 24 hr (Figure 4A), although a strong association with the cell membrane was observed (Figure 4A, white arrows). In comparison, few particles could be found inside the macrophage cells (Figure 4A, yellow arrows), but they were associated with the cell membrane of the macrophage cells (Figure 4B, white arrows). In either case, no changes in the morphology of the cells were observed after being in contact with the THCPSi particles.

Conclusions

The surface chemistry and size of PSi-based materials are parameters to consider in cytotoxicity, cellular association, uptake, and cell permeability. In general, the 1- to 25-µm Psi particles reduced cell viability more than the PSi nanoparticles. No significant production of ROS was observed for the PSi nanoparticles. The THCPSi nanoparticles were associated with the cell membrane and did not permeate significantly through the Caco-2 monolayers. These particles also interacted strongly with the RAW264.7 macrophages, but significant cell uptake was prevented due to the surface properties of the particles. Our investigation demonstrated that by tuning the size and surface chemistry of the PSi particles, different cellular responses can be induced, which can then be used further to enhance drug delivery in a safe and efficient manner.

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Nanoencapsulation Using Microfluidizer® Processors Via "Top Down" and "Bottom Up" Processing Methods

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Microfluidics Corporation, Newton, MA, U.S.A.

Summary
Nanoencapsulation using liposomes, polymers, and emulsions is often used to control delivery of actives, mask ingredient odor or taste, and protect sensitive materials. Microfluidizer® high-shear fluid processors offer two scalable options for nanoencapsulation. "Top down" processing creates a fine emulsion or liposomal formulation by decreasing particle size uniformly. The "bottom up" method, or Microfluidics Reaction Technology™ (MRT), builds particles molecule by molecule as a result of chemical reactions, continuous crystallization, or precipitation. Both types of Microfluidics technology utilize fixed-geometry interaction chambers and have been successful in producing liposomal formulations containing DNA and small molecule drugs, nanoemulsions for cancer drugs and fish oil, and polymer-encapsulated inks.

Introduction
Microfluidics designs and manufactures Microfluidizer® high-shear fluid processors that utilize scalable fixed-geometry interaction chambers and a constant pressure pumping system to achieve efficient nanoencapsulation using polymers, emulsions, and liposomes. Encapsulation is a well-established technique for delivering a range of compounds, such as therapeutics, actives, pesticides, or anti-corrosives, with a number of benefits:

- Control delivery of actives over time
- Protect active materials from oxidation, evaporation, or other sources of degradation
- Decrease potential toxic side effects by preventing high initial concentrations
- Mask the taste or odor of the material

Microfluidics has developed high-shear fluid processors and processing protocols for nanoencapsulation platforms, including nanoemulsions, liposomes, and polymer nanoparticles. Two methods are used to produce such materials: top down and bottom up.

The top down method is used to create nanoparticles by reducing the size of larger particles using high shear and pressure. MRT is used for bottom up production of nanoparticles, molecule by molecule, through chemical reactions and physical processes such as continuous crystallization and precipitation (1). Examples of successful applications are injectables, inhalables, topicals, and parenterals. Specific applications include cancer drugs, anesthetics, non-steroidal anti-inflammatory drugs, vaccine adjuvants, and designer inks.

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Experimental Methods
The core of Microfluidizer® technology is the fixed-geometry interaction chamber, based on an impinging jet design (Figure 1). Fluid inside opposing microchannels may reach flow velocities of 500 m/sec (2). Such jet velocities result in energy dissipation/shear rate levels that are orders of magnitude higher than those of conventional impinging jet devices (3). As a consequence, the mixing scales generated are in the order of 0.020–0.050 µm. Parallel arrays of such microchannels ensure scalability to tens of liters per minute. Energy dissipation levels and shear rates are controlled by the pressure setting and the dimensions of the microchannels.

Top Down
A typical first step is the formation of a pre-mix, which includes all components coarsely mixed together using a rotary-stator or propeller mixer. The pre-mix is then processed in a

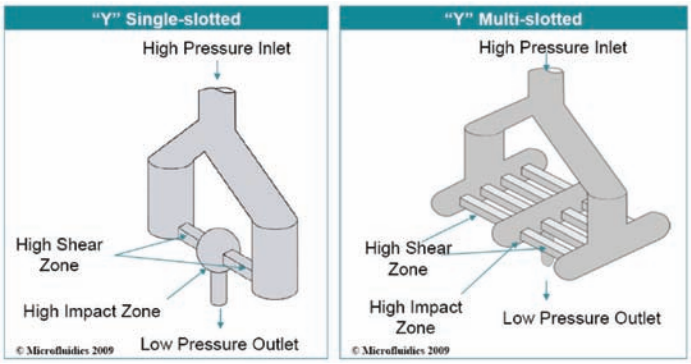

Figure 1. *Schematics of the inside of the Microfluidizer® processor interaction chambers. Left: A schematic of the inside of a single-slotted Y interaction chamber used for laboratory processing. Right: A schematic of the inside of a multi-slotted Y interaction chamber used for industrial processing.*

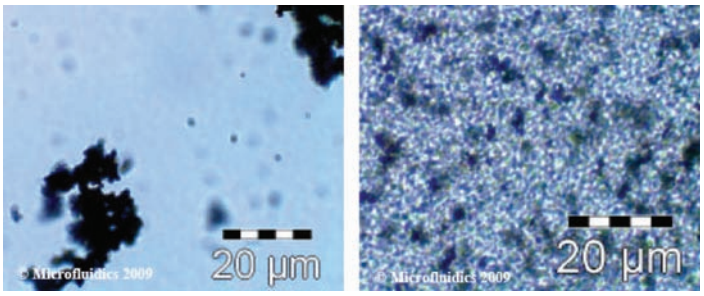

Figure 2. *Microscope images of a carbon black pigment at 1,000× magnification. Left: Particles dispersed in DCM. Right: Particles encapsulated in a solvent and water nanoemulsion after processing with a Microfluidizer® processor.*

Microfluidizer® processor. Desirable results are obtained when the processing parameters (ratios and concentrations of oil, water, active ingredients, and/or surfactants) are optimized for a particular formulation.

The processing conditions of the Microfluidizer® processor (pressure, heating/cooling, number of passes, and interaction chamber type and dimensions) are optimized to provide the appropriate shear rate and thermal profile for the sample. The active ingredient is part of the nanometer-size entities.

Bottom Up

MRT produces nanoparticles by utilizing chemical reactions or physical processes such as crystallization and precipitation. The process described below involves the precipitation of a polymer from a solution by adding a polymer/solvent/API solution to a miscible antisolvent, with oxcarbazepine (CBZ) as the active pharmaceutical ingredient. In a beaker, adding the antisolvent will create a supersaturation condition where the polymer will begin to precipitate out of the mixture. Alternatively, MRT can produce nanoparticles by mixing the two streams inside the interaction chamber at various shear rates by varying the orifice size and processing pressure. Surfactants may be added to stabilize the growth of the nanoparticles and minimize agglomeration of the particles, resulting in a stable suspension.

Results and Discussion

Microfluidizer processors using top down processing were successful in reducing the median particle size of carbon black pigment agglomerates from larger than 10 µm down to encapsulated nanoparticles of 0.695 µm in one pass (Figure 2).

Figure 3. *Omega-3 fatty acids in fish oil were encapsulated in a nanoemulsion. By encapsulating the fish oil, the undesirable taste and smell is significantly reduced, and the oil is protected from oxidation.*

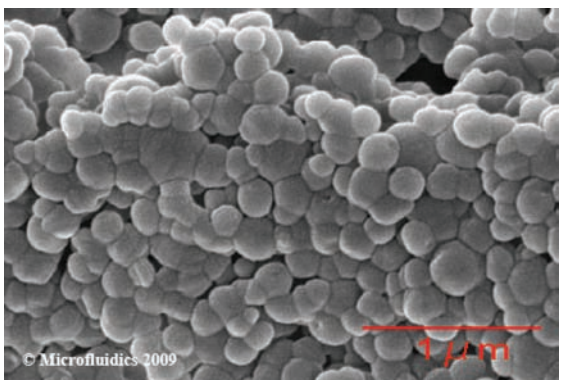

Figure 4. *Microscope images of PCL nanoparticles after processing with a Microfluidizer® processor using MRT.*

Examples of other successful applications included the production of 0.100-µm DNA-loaded liposomes, a 0.050-µm nanoemulsion for the delivery of a cancer therapeutic, and encapsulation of omega-3 fatty acids in a fish oil emulsion (Figure 3).

Using bottom up processing, MRT encapsulated a model drug in polyactide-*co*-glycolide (PLGA) and poly-ε-caprolactone (PCL) (Figure 4). The polymers and CBZ were dissolved in water-miscible organic solvents such as acetone. Water mixed with a non-ionic surfactant was used as the antisolvent phase. The intense mixing of the two streams inside the interaction chamber resulted in co-precipitation of the drug and polymer in the form of nanoparticles.

The nanoencapsulated particles of PLGA and PCL containing CBZ were made with a median particle size of 0.210 and 0.237 µm, respectively. The mixing ratio was 1:3 of solvent/antisolvent with concentrations of 20 mg/mL of the polymers and 5 mg/mL of CBZ in the solvent phase. The encapsulation efficiency ranged from 66.7 to 56.9%, and the final drug concentrations ranged from 25.6 to 12.0%. The ranges were dependant on the initial drug concentration.

Conclusions

Nanoencapsulation of actives in polymers, emulsions, and liposomes was demonstrated using Microfluidics technology platforms and top down and bottom up methods. Carbon black pigment particles of 0.695 µm were produced using the top down method in a nanoemulsion. In addition, DNA was loaded into 0.100-µm liposomes and cancer therapeutics were loaded into 0.050-µm nanoemulsions.

Using MRT bottom up crystallization, PLGA, and PCL polymer nanoparticles containing the drug CBZ were created with a particle size range of 0.210 to 0.237 µm and encapsulation efficiencies as high as 66.7%. Future work will explore additional systems using both technology platforms.

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Gamma Scintigraphy: A Useful Tool in Canine Respiratory Models

L. A. Hodges,[1,2] V. E. Ronaldson,[1] N. Sharma,[1] S. M. Connolly,[1] F. J. McInnes,[3] H. N. E. Stevens,[1,3] C. G. Wilson,[1,3] and G. R. Pitcairn[4]

Introduction

Gamma scintigraphy is widely used in nuclear medicine imaging and has been extensively used in studies on inhaled formulations in humans (1). It is desirable, therefore, to have robust models for such preclinical studies. Canines are widely used in preclinical studies to assess the safety and efficacy of novel inhalation formulations and devices and have previously been used to study mucociliary clearance (2,3). The magnitude of individual variability is important in determining the power and, hence, the number of individual animals needed in such preclinical studies.

The first step toward developing canine respiratory models is to be able to identify the position of the lungs within the dog, as well as the degree of gamma-ray attenuation by bodily tissues. This will allow positional tracking of a labelled formulation within the body and provide tissue attenuation correction factors (ACFs). To be able to utilize canines in preclinical studies on formulations that alter the rate of mucociliary clearance, it is necessary to be able to first demonstrate that gamma scintigraphy can give qualitative and quantitative information on canine mucociliary clearance.

A simple yet robust canine aerosol deposition model has been developed, and the rate of mucociliary clearance in canines has been quantified using gamma scintigraphy.

Results and Discussion

The first goal was to develop a scintigraphic model of aerosol deposition in canines. Attenuation of gamma rays was reduced through lung tissue, as it is less dense than other body tissue. This revealed a lung outline in the scintigraphic image upon positioning the dog between a rectangular technetium-99m (^{99m}Tc) source (approx. 300 MBq) and the gamma camera. The resulting image defined the position of the lungs within the body (Figure 1a). A posterior transmission scan (not shown) showed both lungs.

In order to quantify the tissue ACFs, ^{99m}Tc-labelled macroaggregated albumin (approx. 50 MBq) was administered intravenously. Due to their size (between 10 and 90 μm), the particles accumulated in the lung, the first capillary bed encountered. This enabled the determination of the number of radioactive counts in the lungs by imaging the posterior and lateral thorax (Figure 1b and c). Determination of specific lung activity ratio (lung count rate/radioactivity injected) coupled with the collimator efficiency factor (count rate/activity) provided tissue ACFs (4).

Following development of a canine aerosol deposition model, canine studies were extended to investigate mucociliary clearance rates. Two adult male beagles with permanent tracheostomies were administered ^{99m}Tc-labelled micronized charcoal, and scintigraphic images were recorded at intervals until less than 10% of the initial counts remained in the lungs. Figure 2 shows initial deposition of the charcoal in the lungs in the image taken at 9-min post-dose, followed by accumulation in the trachea after approx. 32 min. After 60 min, emptying into the stomach and small intestine was observed.

By drawing appropriate regions of interest around the lung and whole body for each scintigraphic image, the ratio of lung counts relative to whole body counts was determined for each time point. These values were plotted as lung clearance curves (Figure 3). The red and blue lines are repeats of the same investigational protocol. Although the clearance curves for both dogs were markedly different, they were sufficiently reproducible in each dog; hence each dog could act as its own control for future testing of clearance rate-altering substances.

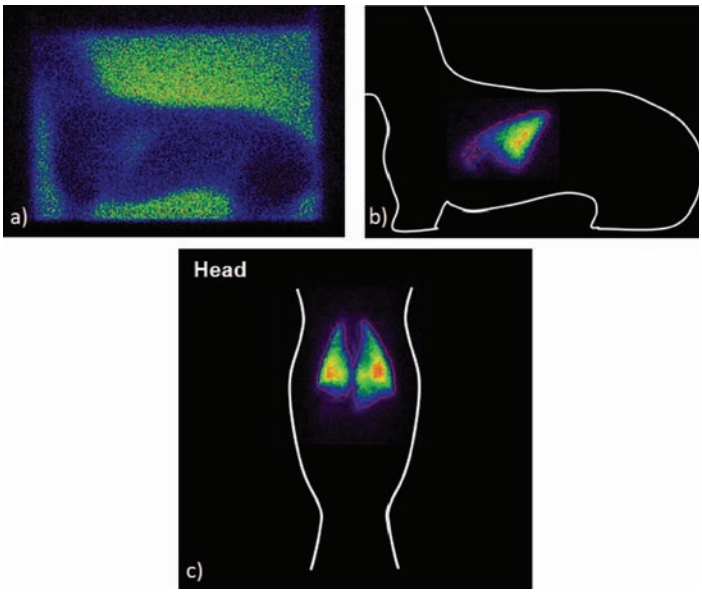

Figure 1. *(**a**) Left lateral transmission scan; (**b**) left lateral scintigraphic image of ^{99m}Tc-MAA accumulation in the lungs with graphic depiction of dog outline; and (**c**) posterior scintigraphic image of ^{99m}Tc-MAA accumulation in the lungs with graphic depiction of dog outline.*

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[3] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, U.K.
[4] Pfizer Global R&D, Sandwich, Kent, U.K.

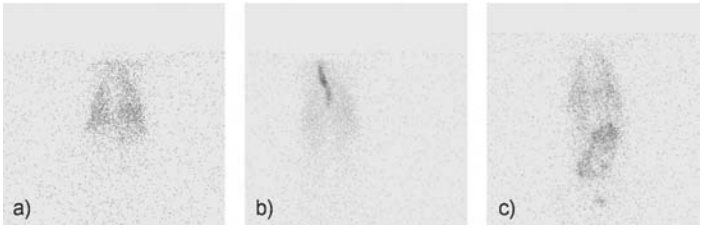

Figure 2. *Scintigraphic images of DOG 1 at* ***(a)*** *9-min post-dose;* ***(b)*** *32-min post-dose; and* ***(c)*** *60-min post-dose.*

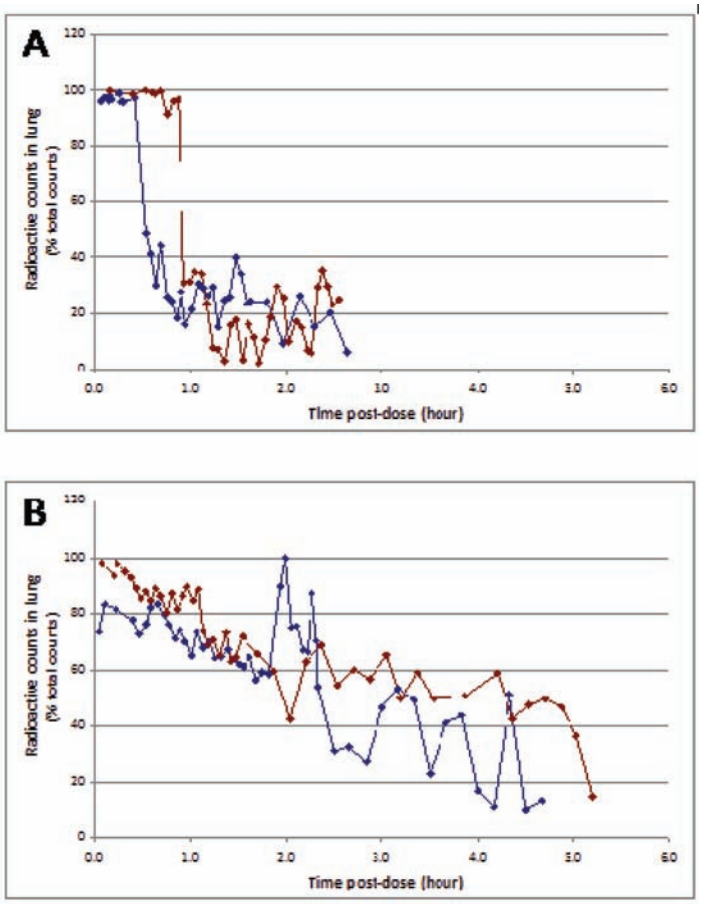

Figure 3. ***A,*** *Lung clearance curves for dog 1; and* ***B,*** *lung clearance curves for dog 2.*

Conclusions

The application of methods previously applied in human clinical studies proved successful in determining canine lung outlines and providing a method for accurate determination of tissue ACFs. A simple mucociliary clearance model was established using ^{99m}Tc-labelled micronized charcoal. This model has the capability of evaluating the effects of substances with the potential to alter mucociliary clearance rates. These studies highlight the utility of gamma scintigraphy, a well-established *in vivo* imaging technique in clinical research, by demonstrating the potential to extend its remit to preclinical canine studies on inhaled formulations.

Acknowledgments

The authors are grateful for the assistance provided by Dr. Michael Wilkinson and Christine Stirton (Biological Services, University of Glasgow).

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A New Title in Veterinary Drug Delivery

The topics addressed in the new volume of *Comparative and Veterinary Pharmacology*, as a series of succinct state-of-the-art reviews, illustrate both the commonality and differences between drug pharmacodynamics and pharmacokinetics in animals and humans and demonstrate the potential impact of drug use in animals on human health and the environment. Genetic modification of animals and the benefits this has brought to understanding human diseases and the production of drugs for use in humans is considered, and the potential of new technologies for improving the treatment of animal disease is explored (www.springer.com). The new volume will be available April 3, 2010.

Publication Information

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Contents

Abstract

Delivery of biologically active agents to animals is often perceived to be the poor relation of human drug delivery. Yet this field has a long and successful history of species-specific device and formulation development, ranging from simple approaches and devices used in production animals to more sophisticated formulations and approaches for a wide range of species. While several technologies using biodegradable polymers have been successfully marketed in a range of veterinary and human products, the transfer of delivery technologies has not been similarly applied across species. This may be due to a combination of specific technical requirements for use of devices in different species, inter-species pharmacokinetic, pharmacodynamic and physiological differences, and distinct market drivers for drug classes used in companion and food-producing animals. This chapter reviews selected commercialised and research-based parenteral and non-parenteral veterinary drug delivery technologies in selected domestic species. Emphasis is also placed on the impact of endogenous drug transporters on drug distribution characteristics in different species. *In vitro* models used to investigate carrier-dependent transport are reviewed. Species-specific expression of transporters in several tissues can account for inter-animal or inter-species pharmacokinetic variability, lack of predictability of drug efficacy, and potential drug–drug interactions. ■

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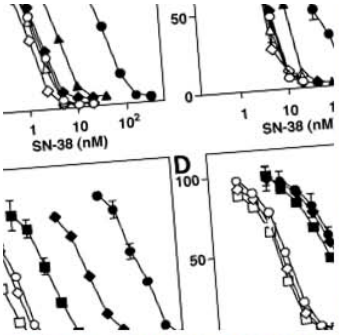

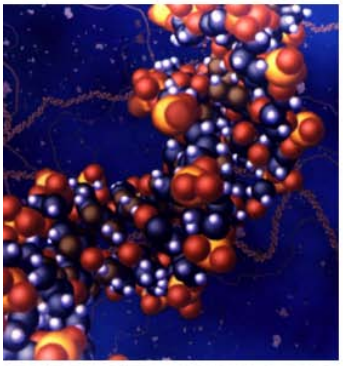

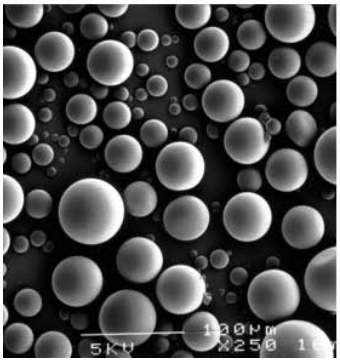

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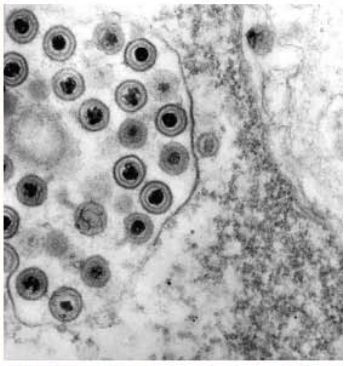

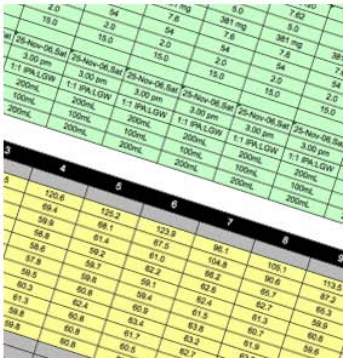

CRS Illinois Student Chapter Holds '80s Game Night

The CRS Illinois Student Chapter hosted a social event sponsored by the University of Illinois at Chicago (UIC) on October 15, 2009, at the UIC College of Pharmacy building. The event was an '80s game night organized to provide a break from work and studies for some fun and socializing with CRS IL. Attendees played popular games from the 1980s, ranging from Trivial Pursuit to Nintendo Pac Man, while listening to music from the era. The event concluded with the presentation of door prizes that included two free memberships to CRS. Approximately 40 students and post-docs from a variety of departments, including Bioengineering, Biopharmaceutical Sciences, Medicinal Chemistry and Pharmacognosy, and Pharmacy attended the event. The CRS Illinois Student Chapter has doubled in size since last year and currently has 47 members from the Illinois Institute of Technology, Loyola University, the University of Illinois at Chicago, and the University of Michigan Ann Arbor. The chapter plans a seminar and a one-day symposium for spring 2010. Recent news of the CRS Illinois Student Chapter can be found at www.crsillinois.com. ■

CRS-Illinois Student Chapter members enjoy a trip to the '80s.

Joint Meeting of PAT2009 and the CRS Israeli Chapter

Prof. Rosa Azhari
President of CRS Israeli Chapter

The CRS Israeli Chapter was a cosponsor of the PAT2009 meeting in Jerusalem. Innovations in drug delivery and related topics were presented in three drug delivery sessions and in plenary lectures. More than 80 members of the Israeli Chapter took part in the meeting.

The meeting was opened with a lecture by Nobel Laureate Prof. Israel Aumann, a mathematician who demonstrated the relevance of basic mathematical research on knots to the analysis of interacting polymer chains. Andreas Lendlein described the use of novel, shape memory, biodegradable block copolymers in regenerative medicine and delivery of bioactive compounds, and Virgil Percec (University of Pennsylvania) described bio-inspired synthesis of dendritic macromolecular systems from self-assembling building blocks.

Prof. Dror Deliktar (Technion) discussed the use of methacrylated PEG and natural polymers conjugates for *in situ* formation of scaffolds for tissue regeneration, and Smadar Cohen (Ben-Gurion University in Beer-Sheva) described the development of instruction materials for inducing angiogenesis and tissue regeneration. The drug delivery session was opened with a keynote address by Avri Rubinstein (Hebrew University of Jerusalem) discussing opportunities in colon-specific drug delivery, drug absorption opportunities, and treatment of inflammatory bowl diseases and colorectal cancer. In addition, he described novel methodologies for colorectal cancer diagnosis.

Dan Peer (Tel-Aviv University) described the delivery of SiRNA to leukocytes using hyaluronan-coated nano-vesicles targeted to various receptors on the cell surface. Applications for treatment of inflammatory bowl diseases were detailed. The use of liposomes derived from cell membranes and conjugated to CCR, for anti-retroviral therapy was the topic of the presentation by Tomer Bronstein (Technion). Nissim Garti (Hebrew University of Jerusalem) described his work on double emulsions and their application in nutraceuticals delivery, with a focus on stabilization using complexes of proteins and hydrocolloids.

Prof. Avri Rubinstein (left) and Prof. Rosa Azhari (right) present the first prize for the CRS Israeli Chapter student poster competition to Tomer Bronshtein (Technion, Israel Institute of Technology).

Emil Rubinov (Ben-Gurion University in Beer-Sheva) described the delivery of bioactive HGF to infracted cardiac regions using an injectable biomaterial and the resulting prevention of increased angiogenesis and apoptosis and infarct expansion. Yoav Livney talked about the use of arabinogalactan-folate drug conjugates for targeting anti-cancer drugs to folate receptor-expressing cancer cells. Ronit Satchi-Fainaro described the use of multivalent polymers, for a cancer therapy that combines targeting, anti-angiogenic agents, and chemotherapy. *In vitro*- and *in vivo*-enhanced effects were demonstrated in breast cancer, prostate cancer, and bone metastases.

Ravi Kumar described the potential of biodegradable nanoparticles for peroral delivery of poorly soluble drugs, and Wahid Khan talked about the characterization and evaluation of paromomycin-loaded albumin microparticles in treatment of visceral leishmaniasis. Yechezkel Barenholz, one of the inventors of DOXIL™ (doxorubicin in liposomes), an anticancer drug and the first liposomal drug approved by the US FDA in 1995, discussed the advantages and limitations of liposomal drugs and showed how the success and failure of drugs are related to system physicochemical properties. Neeraj Kumar described the use of brush-type amphiphilic copolymers for the formation of polymersomes able to deliver hydrophilic and hydrophobic agents. Gershon Golomb described the use of nanoparticles in modulation of innate immunity. The session was closed with a presentation by Ayelet David on polymer-peptide drug conjugates for targeting tumor vascular endothelium.

The winners of the 2009 student presentation contest held during the PAT2009 meeting were

First Prize
Daniel Zucker, "Cancer Therapeutic Efficacy of Two Drug Combination Co-remote Loaded into Nanoliposomes: Relevance of *In-Vitro* Synergy" (supervised by Prof. Ychezkel Barenholz, Hebrew University of Jerusalem)

Second Prize
Ehud Segal, "RAFT—Synthesized Nanoconjugates for Targeting Bone Metastases and Calcified Neoplasms" (supervised by Dr. Ronit Satch-Fainaro, Tel Aviv University)

Third Prizes
Emil Rubinov, "Affinity-binding Alginate Biomaterial for the Controlled Delivery of Cardiovascular-Protective Factors" (supervised by Prof. Smadar Cohen, Ben-Gurion University of the Negev, Beer-Sheva)

Eva Kopansky, "Polymer Conjugates for Visualizing Solid Tumors in the GI Tract" (supervised by Ayelet David, Ben-Gurion University of the Negev)

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Lior Raviv, "Mannosylated Block Copolymer Micelles for Targeting Genes into Antigen-presenting Cells" (supervised by Ayelet David, Ben-Gurion University of the Negev).

During the PAT2009 Gala dinner, prizes for student poster presentations were given to the winners of the competition held during the 6th Annual Meeting of the CRS Israeli Chapter. Tomer Bronshtein (Faculty of Biotechnology Engineering, Technion, Haifa) was awarded first prize for his presentation "CCR5-Conjugated Proteo-liposomes as a New Drug Delivery System to HIV Reservoir Cells and Free Virion Entrapment" (supervisor: Prof. Marcelle Machluf); Oded Ovadia (Hebrew University of Jerusalem) was awarded second prize for his presentation, "Permeability and Pharmacological Activity of Backbone Cyclic Peptides: The Effect of N-Methylation (supervisor: Prof. Amnon Hoffman); and third prize was awarded to Margarita Shumilov (supervisor: Prof. Elka Touitou, Hebrew University of Jerusalem), Ehud Segal (supervisor: Dr. Ronit Satch-Fainaro, Tel Aviv University), and Avi Schroeder (supervisors: Prof. Joseph Kost, Ben Gurion University, and Prof. Yechezkel Barenholz, Hebrew University of Jerusalem). ■

Welcome CRS Student Chapter The Hebrew University of Jerusalem

The new CRS Student Chapter The Hebrew University of Jerusalem was officially recognized on January 1, 2010. Following is a list of the current members. For detailed contact information, please visit the chapter's webpage at www.controlledreleasesociety.org/main/chapters/chapterdetail.cfm?ID=STUDENTHUJI.

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CRS Italian Chapter

The annual CRS Italian Chapter workshop was held in Modena, Italy, November 5–7, 2009. The subject of the workshop, "Multidisciplinary Strategies to Target the Central Nervous System," attracted more than 130 delegates from both academia and industry, including a few international scientists. Thanks to CRS and a few other sponsors it was possible to support the participation of CRS members, young scientists in particular. Furthermore, the workshop was broadcast to more than 300 contacts. Full registration is now available on the website (www.tv.unimore.it/media/medicina/vandelli/index.html).

At the opening, the co-chair of the workshop, Prof. Vandelli (University of Modena), and the CRS Italian Chapter president welcomed the delegates and discussed the upcoming local and international CRS activities. The attendees were warmly invited to provide advice on and join the minisymposium on oral delivery ("Towards Drug Delivery Systems: When the Drug Doesn't Like the Standards," Milan, December 2, 2009), the CRS-AFI ("Innovation in Pharmaceutical Products and Processes" Rimini, June 10, 2009), and, in particular, the CRS Annual Meeting (Portland, OR, July 10–14, 2010).

The CRS Italian Chapter president introduced the workshop by underlining the aims of the association: education of young and senior scientists through the dissemination of drug delivery knowledge from multidisciplinary perspectives; promotion of

industrial and academic collaborations; and creation of effective scientific national and international networks. The attendees then were encouraged to participate as main actors in the workshop, which was organized in a familiar atmosphere to make everybody, young scientists in particular, feel comfortable, free to ask any questions, and to contribute to the discussion.

The workshop program continued with the scientific sessions, which were excellently directed by the chairs, who stimulated audience contributions. Outstanding Italian and international scientists were invited to highlight the interdisciplinary character of brain delivery. Biological mechanisms and clinical aspects of neurodegenerative diseases, CNS-related malignancies, hematologic and Huntington disease were presented by Prof. Agnati and Dr. Riva (University of Modena) and Prof. Cattaneo (University of Milan). Prof. Delie (University of Geneve) described the use of an *in vitro* blood brain barrier model as a reliable tool for brain delivery studies. The development and exploitation of HIV-1 viral protein Tat and vectors for receptor-mediated transcytosis in brain delivery were reported by Prof. Pittaluga (University of Genua) and Prof. Khrestachatisky (University of Marseille), while Prof. Masserini (University Bicocca, Milan) and Prof. Constantino showed the use of nanoparticles in brain targeting and Alzheimer disease. On the industrial side, Dr. De Santis (Sigma-Tau) disclosed the results obtained in collaboration with the European Institute of Oncology on avidin-biotin systems for brain targeting. Dr. Benichou (Genzyme) and Dr. Gaviraghi (Siena Biotech) described the industrial strategies and platforms for CNS disease targeting and identification of new brain-penetrating drugs.

The main lectures introduced a variety of scientific reports from senior and young scientists on the use of drug delivery systems for brain targeting. Dr. Esposito (University of Ferrara), Dr. Brioschi (Italian Auxol Institute of Turin), Dr. Craparo (University of Palermo) and Dr. Vighi (University of Modena) presented the results obtained with lipid nanoparticles. The use of polymeric nanoparticles, mainly based on chitosan derivatives, were reported by Dr. Trapani (University of Bari), Prof. Dal Piaz (University of Ferrara), and Dr. Mennini (University of Florence). Liposomes and niosomes for brain delivery were shown by Dr. De Rosa (University of Naples) and Dr. Bragagni (University of Florence). Bioconjugation strategies to enhance drug delivery in the central nervous system were reported by Dr. Iannitelli (University of Chieti) and Dr. Denora (University of Bari). Dr. Salmaso (University of Padua) showed the results obtained with ascorbic acid as a targeting agent, while Prof. Fresta (University of Catanzaro) reported results obtained by his research group in an *in vivo* study for the BBB passage evaluation of a colloidal drug delivery system. Finally, Dr. Poggi (Bracco Imaging) and Prof. Smith (University of Aarhus) presented brain imaging by magnetic resonance and positron emission tomography.

Prof. Vandelli, Prof. Fresta, and Dr. Bragagni were charged with the concluding remarks. On behalf of the CRS Italian Chapter, Prof. Fresta thanked Profs. Vandelli and Forni, Drs. Tosi and Ruozi, and all the staff of the University of Modena, including students, for the excellent organization and logistical support provided for the delegates. Dr. Bragagni, as a representative of the young scientists, gave positive comments and thanked everyone for their efforts to involve all attendees in the activities.

The workshop was dedicated to the memory of Maria Edvige Sangalli, Didi, treasurer of the CRS Italian Chapter, colleague, and friend. ■

CRS New Zealand and Australian Chapters Hold Workshop on "Improving the Bioavailability of Poorly Water-Soluble Drugs"

Ulrike Zimper and Pegah Varamini

A Controlled Release Society two-day workshop tackling solubility-related formulation issues was held in Brisbane, Australia (November30–December 1, 2009), and Auckland, New Zealand (December 3–4, 2009), attracting more than 45 delegates in Brisbane and 50 participants in Auckland. The workshop was led by Australasia's leaders in the field, including Prof. Istvan Toth (The University of Queensland), Prof. Thomas Rades (The University of Otago), Dr. Raid Alany (The University of Auckland), and Dr. Ben Boyd (Monash University), with the aim of discussing cutting-edge approaches to formulation design to improve the bioavailability of poorly water-soluble drugs. More than half of the workshop participants were students from different universities (not only from Australia and New Zealand), as well as from industry. Hence, this workshop offered ideal opportunities to initiate

Workshop speakers in Brisbane (left to right): Dr. Jingyuan Wen, Dr. Raid Alany, Prof. Istvan Toth, Dr. Anja Graf, Dr. Ilva Rupenthal, Dr. Pavla Simerska, and Dr. Ben Boyd. Photo by Pegah Varamini.

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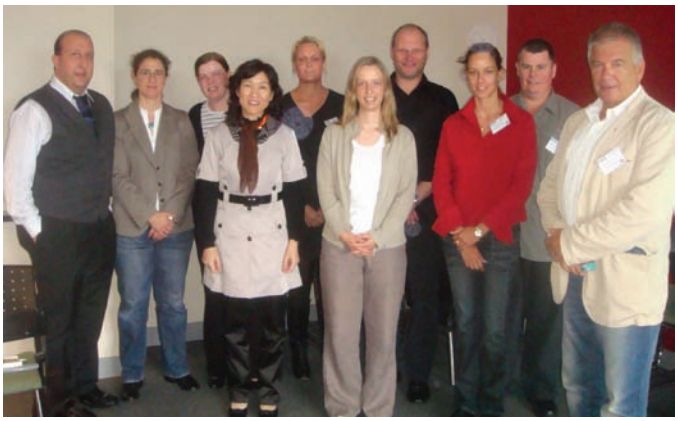
academic and industrial cooperation, as well as inter-academic collaboration.

There were more than 10 speakers, including Prof. Istvan Toth and Dr. Pavla Simerska (The University of Queensland); Prof. Thomas Rades, Dr. Anja Graf, Dr. Simon Young, and Dr. Clare Strachan (The University of Otago); Dr. Raid Alany, Dr. Zimei Wu, Dr. Ilva Rupenthal, and Dr. Jingyuan Wen (The University of Auckland); Dr. Ben Boyd (Monash University); and Dr. Karen Krauel-Goellner (Massey University).



Workshop speakers in Auckland (left to right): Dr. Raid Alany, Dr. Karen Krauel-Goellner, Dr. Clare Strachan, Dr. Zimei Wu, Dr. Ilva Rupenthal, Dr. Anja Graf, Prof. Thomas Rades, Dr. Pavla Simerska, Dr. Ben Boyd, and Prof. Istvan Toth.

Audience at the workshop in Auckland. Photo by Raid Alany.

After the workshop was opened by NZ-CRS Chapter President Dr. Raid Alany in Auckland and Dr. Pavla Simerska in Brisbane, all aspects of dissolution were put into focus by Dr. Ben Boyd during his first presentation. Subsequently, different means to improve the dissolution rate were discussed by the following speakers: Dr. Clare Strachan presented polymorphic and co-crystal formulation as one possible pathway to better dissolution, Dr. Anja Graf highlighted lipid systems as a formulation approach, and Dr. Karen Krauel-Goellner highlighted nano-crystal formulation approaches. Dr. Pavla Simerska gave insights into chemical modification possibilities in order to improve bioavailability, and Dr. Zimei Wu talked about aspects of cyclodextrin formulation. Finally, Dr. Simon Young presented colonic targeting as a means to improve bioavailability.

After the final session, participants were divided into small groups to discuss and share their ideas and expertise on some case studies allied with different ways of improving the bioavailability of poorly water-soluble drugs. A round-table discussion, followed by the workshop dinner, concluded the first day both in the Auckland and Brisbane workshops.

The first session on day two was an instrument demonstration and included a laboratory tour. Different instruments, such as LCMS, DSC (differential scanning calorimeter), and nanosizer primarily employed for characterization of peptide and protein formulations, were demonstrated.

Instrument demonstration in Brisbane (left to right) by Dr. Mingtao Liang (Nanosizer), Dr. Zita Ziora (DSC,) and Julie Bergeon (LCMS). Photo by Pegah Varamini.

The second day of the workshop was opened by Prof. Thomas Rades in Auckland and Dr. Pavla Simerska in Brisbane and was followed by Prof. Istvan Toth's presentation on vaccines and oral delivery. Prof. Thomas Rades continued with a lively presentation of solid solutions as a pathway to increased dissolution. Dr. Jingyuan Wen presented her graduate work dealing with oral absorption of peptides. After the very enjoyable lunch, provided by the industrial sponsors (Argenta, Alphatech, Dionex, and BOMAC), the day proceeded with the last session, which included three talks. Dr. Ilva Rupenthal gave a presentation on improving the bioavailability of oligonucleotides, followed by Dr. Raid Alany, who discussed oral permeability issues of class IV drugs. The last talk of the workshop included a summary of testing methods for poorly water-soluble drugs, which was given by Dr. Ben Boyd.

Participants at Brisbane CRS workshop. Photo by Pegah Varamini.

The workshop in Brisbane was closed by Dr. Simerska, who thanked everybody for their participation, and in Auckland an on-site instrument demonstration closed this very successful workshop.

Finally, we would like to thank the sponsors of the workshop for their generous help and support: Alphatech, Ancare, Argenta, BOMAC, Dionex, Tetra, The University of Auckland, The University of Otago, and The University of Queensland. ■

CRS-AAPS Satellite Workshop a Resounding Success

Ron Ortiz, Ph.D.,[1] and Dody Reimer, Ph.D.[2]

The second satellite workshop held under the joint auspices of two organizations—the Controlled Release Society (CRS) and American Association of Pharmaceutical Scientists (AAPS)—was held November 7–8, 2009, in Los Angeles, CA, in conjunction with the AAPS Annual Meeting. The workshop, entitled "Development and Regulatory Challenges for Controlled Release Formulations," was generously sponsored by Northern Lipids, Inc., 3M Drug Delivery Systems, LTS Lohmann Therapie-Systeme AG, Eurand Pharmaceutical Technologies, Colorcon, and Polymune Scientific GmbH. The workshop highlighted 11 presenters, all experts in their field, from industry and regulatory agencies. Based on the stimulating discussions, audience participation, and positive feedback from many attendees, the organizers are pleased to announce that the workshop was considered a huge success, drawing in excess of 75 participants.

The event was an initiative organized by the CRS Young Scientist Committee. This year's organizers were Dody Reimer (Northern Lipids), Avinash Thombre (Pfizer), Louise Rosenmayr-Templeton (Tower Pharma Consulting), and Ron Ortiz (Upsher-Smith Labs). The goals of the workshop were to

1. Provide an understanding of the developmental and regulatory challenges for controlled release formulations utilizing mature and evolving new technologies in Europe and North America.
2. Provide a venue for young and/or established scientists to meet informally with other scientists and regulatory authorities.
3. Share and discuss fundamental science and experiences that may be of value to individuals dealing with various controlled release technologies.
4. Gain an understanding of the differences between the regulatory bodies of the EU and the FDA.
5. Increase an individual's knowledge about a variety of controlled release technologies that may not be found in the literature through shared experiences and panel discussions.
6. Apply newly acquired knowledge and a suitable approach to the potential design of the attendees' own pharmaceutical products.

The workshop was organized into two sessions over two days: 1) Mature CR Technologies, and 2) Emerging CR Technologies.

1) Mature CR Technologies

The workshop was kicked off on day one by a stimulating presentation by Michael Palmieri (Alkermes), entitled "The Challenges During the Development of Long Acting Injectables." Michael reviewed the development process and challenges that Alkermes overcame in bringing a number of long-acting injectable products to market. Michael presented the background of the long-acting injectable technology, an overview of the manufacturing process, and factors to consider when designing release- and stability-testing specifications for such systems.

Workshop organizers Ron Ortiz and Dody Reimer.

The second speaker of the session was Richard Green (Pfizer), who presented a talk on "Orally Disintegrating Tablets." Richard started his talk by reviewing orally disintegrating tablet (ODT) technologies and the ODT market landscape. He highlighted the delicate balance between structure and function when selecting ODT components and technology. He also educated the group regarding the development challenges in the ODT arena, especially those pertaining to pharmacokinetic performance, physical properties, and taste masking.

The morning session finished strongly with speaker Elaine Liversidge (Élan Drug Technologies) delivering her presentation, entitled "The Development History of NanoCrystal® Products: A Ten-Year Perspective." Elaine presented a comprehensive overview of the NanoCrystal® technology, covering its history and evolution, products that utilize the technology, and new opportunities and innovations to come. Elaine also highlighted some of the challenges, both regulatory and development related, associated with introducing a new processing technology to the pharmaceutical industry.

Following the first three presentations, the audience and morning speakers participated in a lively panel discussion with plenty of thought-provoking questions and comments from the attendees. A well-attended networking lunch followed the discussion, which enabled many opportunities for speakers and attendees to mingle and engage in additional discussions.

The afternoon session began with Tom Redelmeier (Northern Lipids, Inc.) addressing "Developmental and Regulatory Challenges with Liposomes." Tom outlined a formulation strategy for identifying liposome prototypes to take into development. Tom also identified factors that are important from a CMC perspective when designing clinical development programs. He summarized his talk by pointing out that liposome

[1] Upsher-Smith Laboratories, U.S.A.
[2] Northern Lipids, Inc., Canada.

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technology is a mature science where many of the development and regulatory challenges have been previously observed and that a systematic investigation at each stage of drug development is critical to advancing a program quickly.

Michael Horstmann (LTS Lohmann Therapie-Systeme AG) presented the next talk, titled "Development and Regulatory Challenges Associated with the Transdermal Delivery of Small Molecules." Michael reviewed the *in vitro* release and permeation models traditionally used in transdermal product development and highlighted some of the strengths and limitations associated with each model. He engaged the audience with some discussion on the relevance (or lack thereof) of *in-vitro/in-vivo* correlations and the applications of this approach in transdermal delivery.

The presentations and discussions around mature CR technologies from the first day were brought together in the concluding presentation of Aidan Madden (FivePharma). Aidan energetically presented the process of "Carrying Out Early Phase Clinical Trials in the EU on Non-EU Produced Investigational Medicinal Products." In particular, Aidan ambitiously covered the topic of importation into the EU and the challenges related to Qualified Person certification. During the course of his presentation, Aidan gave a historical perspective on factors that have influenced today's importation and release processes and brought the attendees up-to-date on current importation considerations. The first day was concluded with another engaging panel discussion that included the afternoon speakers.

2) Emerging CR Technologies

The second day focused on emerging technologies. The session was kicked off by Laurens van Pinxteren (OctoPlus NV). Laurens's talk, entitled "Developmental and Regulatory Challenges with Interferon Microparticles—Locteron," shared OctoPlus' experience with the development of a double-emulsion microsphere product. Laurens covered the technical challenges associated with protein stabilization, as well as the regulatory challenges encountered by controlled release carrier systems. He pointed out that the regulatory challenges associated with microspheres must be considered at the earliest stages of product development.

The next presentation of the session was from Gopi Venkatesh (Eurand). Gopi addressed "Technical and Regulatory Challenges Associated with Diffucaps Drug Delivery Systems." Gopi highlighted the advantages of once daily administered multiparticulate systems and also addressed their associated development challenges. He presented two case studies in the use of Diffucaps for chronotherapy: one on InnoPran XL and the associated release profiles and the other on EUR-1025 Ondansetron and the unique properties this formulation in an acidic pH environment.

The third speaker of the session was Mark Tracy (Alnylam), who spoke on the subject of "Development of RNAi Therapeutics." Mark presented a background of RNA interference (RNAi) and general considerations when developing RNAi therapeutics. Mark nicely put into context some of the CMC differences between traditional small molecules and RNAi development candidates and the complexities that come with these types of formulations. Of course, the challenges with these types of formulations remain their effectiveness in improving delivery and ability to target sites of disease. Many opportunities now exist for RNAi therapeutics, and multiple disease targets can be achieved simultaneously.

The morning session on day two was brought to a close with another engaging panel discussion, followed by a networking luncheon for the workshop participants and speakers. Participant feedback on the panel discussion and networking opportunity was very positive.

The first of two afternoon speakers was Kevin Harper (Sanofi-Pasteur). Kevin shared the challenges faced in vaccine formulation development in his presentation, entitled "Controlled Release and Immunogenicity—A Vaccine Perspective." Kevin reviewed important antigen and adjuvant characteristics and how the immune system responds to each. The presentation highlighted how various controlled release technologies (liposomes, nanoparticles, etc.) can impact pharmacological responses and may pose unique development challenges.

The last session of this two-day venture was presented by Patrick Marroum (FDA) who provided examples of regulatory challenges and past findings on products utilizing controlled release technologies. Patrick's talk, entitled "The Science and Regulatory Perspectives of Controlled Release Products with Emerging Technologies," was well received and focused on the bioavailability/bioequivalence considerations for modified release dosage forms. Patrick provided definitions for various controlled release (CR) dosage forms, a comparison of NDA and ANDA requirements for CR products, and included real-world examples of CR products and what it took from a regulatory perspective to bring them to market. Following Patrick's presentation, the organizers opened the floor to some stimulating discussions with plenty of questions, contributions, and opinions that arose from attendees representing a variety of backgrounds. The panel discussion provided an excellent conclusion to the workshop.

In summary, the second CRS-AAPS Joint Satellite Workshop was an astounding success. The impressive attendance gives testament to the immense interest in workshops that combine the developmental challenges of technology with input on how to meet regulatory needs, an area that will undoubtedly continue to be important as more products are brought to the market. The 2010 planning committee is now seeking input for future satellite workshop topics and themes. Please let us know what topics are of most interest to you. If you have an idea for future satellite workshops contact this year's Committee Co-chair Dody Reimer (dodyreimer@northernlipids.com). ■

News from the CRS Nanomedicine Focus Group

Hamid Ghandehari,[1] Dusica Maysinger,[2] and Claus Michael Lehr[3]

The convergence of recent advances in nanotechnology with modern biology and medicine has created the new research domain of nanobiotechnology. The use of nanobiotechnology in medicine is termed nanomedicine. Nanomedicine research includes, but is not limited to, the development of diagnostics for rapid monitoring, targeted cancer therapies, localized drug delivery, improved cell-material interactions (e.g., for tissue engineering), and the delivery of macromolecular biologicals (e.g., peptides, proteins, nucleic acids) across biological barriers. The emerging need to establish focal points of multidisciplinary research for the development of modern functional nanosystems for use in medicine has been recognized in the scientific community and by countries around the globe (1,2). The Controlled Release Society is in a unique position to foster collaborative research in nanomedicine. Since its inception over 35 years ago, CRS members have worked on developing numerous nanoscale systems for delivery of bioactive agents. Examples of such delivery systems include water-soluble polymers; polymeric, liposomal, or hybrid nanoparticles; and polyethylene glycol–protein conjugates, among others.

Advances in nanotechnology over the past decade have provided new and unique opportunities for scientists interested in controlled release. For example, unique technologies have emerged that enable us to control the geometry and size distribution of particles that did not exist before (3). Control over geometry influences biodistribution, cellular uptake, degradation, etc. New "bottom up" and "top down" nanofabrication approaches have led to the development of nanostructures where their physicochemical properties can be controlled by changing their aspect ratio (e.g., gold nanorods [4]) or they can be differentially functionalized to allow tuning biocompatibility and drug loading (e.g., silica nanotubes [5]). Other examples include design and development of nanofibers for tissue-engineering approaches (6) or self-assembled structures such as polymersomes (7). Combining the lessons learnt from the first prototype nanoscale drug delivery systems with new advances in the design and characterization of novel well-defined nanoconstructs can be powerful in the development of future generations of controlled delivery systems.

With that in mind the CRS Nanomedicine Focus Group was launched during the 2008 CRS Annual Meeting in New York to advance the mission of the Society by promoting the science, technology, and innovation of delivery of bioactives using nanoscale constructs. The proposed activities of the Nanomedicine Focus Group during its first membership meeting were to organize nanomedicine roundtables and workshops, identify possibilities of alliance with other global nanomedicine meetings, coordinate efforts with the *Journal of Controlled Release* to potentially publish theme issues or articles in this field, create a nanomedicine "corner" or "column" in the *CRS Newsletter* to publish the latest news or research in this area, and promote education and advocacy in regulatory affairs by interacting with member country regulatory agencies, among other activities.

The first Nanomedicine Roundtable, co-organized by Ghandehari (chair of the focus group) and Maysinger, took place during the 2009 CRS Annual Meeting in Copenhagen with the theme "Nanomedicine: From Materials Design to Living Cells and the Clinic." Followed by a brief introduction by the co-organizers, the first speaker, Dr. Wallace Akerley of the University of Utah Huntsman Cancer Institute (USA), a medical oncologist by background, gave an inspiring presentation emphasizing the limitations in early detection and effective treatment of cancers. His "clinician oncologist's nanomedicine wish list" included the need for developing technologies to enable small sample diagnosis, identify molecular markers of pathway modulation, allow measurement of tumor volume and organ function, enable new mechanisms of cell kill, and improve tumor-specific imaging and delivery. While Dr. Akerley's talk focused on unmet needs in cancer treatment and diagnosis, the second speaker, Dr. Terry Allen of the University of British

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Columbia (Canada), provided an impressive historic overview of the design and development of liposomal delivery systems and highlighted the hurdles and limitations of liposomes along the way, from the basic science research bench to Phase III clinical trials. Key questions raised by Dr. Allen that stimulated discussions included the following: Would longer half-life stealth liposomes be desirable for delivery to tumors? Is it possible to develop rapid release delivery systems that have improved therapeutic outcomes over free drugs, or over sustained release systems? Will ligand-targeted drug delivery systems increase the therapeutic outcome sufficiently to make up for the increased expense and complexity of the systems? Are there advantages/disadvantages of having two or more ligands on the same particle versus physical mixtures of individual ligand-bearing particles? Are combination targeting strategies going to be too complex or too expensive for the clinic? In contrast to the first two speakers whose research was tightly linked to the clinical problems in oncology, the third speaker, Dr. Paul DeKonnick of the University Laval (Canada), presented highly advanced approaches for imaging physiological events in single neurons. To this end he utilized small, brightly fluorescent quantum dots to show that they can be used to investigate synaptic remodeling. Nano-neuroscience is in its infancy, and only a very limited number of laboratories in the world could achieve such a level of resolution to show how normal and sick neurons can communicate and change their shape and size during this communication process in the brain. Although, there are no data from the clinical studies using fluorescent nano-probes that emit in the near infrared region, the preclinical experiments in animals mimicking some neurological disorders point toward nanomedicines as viable means of detection and therapeutic intervention in diseased nervous systems.

For the 2010 CRS Annual Meeting in Portland, OR, two events are being organized by the Nanomedicine Focus Group: a workshop on Saturday, July 10, and a roundtable on Sunday, July 11. Immediately after the roundtable, the attendees at the CRS convention are invited to join the focus group member meeting and provide input for its activities and future planning. Stay tuned for more details.

Note: Questions or comments about the CRS Nanomedicine Focus Group can be addressed to the co-authors of this article.

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CRS Oral Drug Delivery Focus Group Update

The CRS Oral Drug Delivery Focus Group will offer a roundtable on "Can One Size Oral Dosage Form Fit Different Patient Populations?" during the 2010 CRS Annual Meeting in Portland, OR, Sunday, July 11 between 09:00 and 11:00.

We are looking forward to an interactive session, exchanging ideas among like-minded people, and coming up with some answers, as well as a better path for future oral drug delivery developments. This roundtable will focus on variation in age, sex, and ethnicity that may lead to alternation in drug dosing, metabolism, and efficacy. These variations have important implications for the drug development process. Brief presentations will be given on the key question: Does one size fit all? We will hear from experts about the variation in human physiology and its effects on oral dosage forms; how new technologies may address some of the barriers associated with oral delivery; and how dosage form variation and device development can fit into a regulatory agency's guidelines for approval. Following the presentations, we will have a round-table discussion to consider and debate the presented points of views and perspectives.

Co-chairs:
Dr. Sarah Eccleston (University of Strathclyde)
Dr. Kristy Ainslie (Ohio State University)

Confirmed panel speakers:
Prof. Clive Wilson (Strathclyde University)
Dr. Tejal Desai (University of California, San Francisco [UCSF])
Dr. Lawrence Yu (FDA) ■

Welcome New Members

Hazem M. S. Abdelkarim	Cindy Muxin Liu
Ayse Acma	Joseph M. Manak
Adah Almutairi	Kathy C. Meserve
Eddie L. Brunson	Serhan Rende
Ruth Castillo	Rohit Srivastava
James J. Cunningham	Suhair Z. Sunoqrot
Fengqui Fan	Kailas Thakker
Li Feng	Kevin Zen
Seongbong Jo	Qinghe Zhao

CRS Delivering Bioactives

Consumer and Diversified Products

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

The following patents were issued from July through December 2009. Included in this summary are patents that involve controlled release directly or potentially in a consumer and diversified product area such as food, flavor, cosmetic, fragrance, personal care, household product, agriculture, or pest control. The principle search engines used for this summary were the U.S. Patent Office website (www.uspto.gov) for U.S. patents and the European Patent Office website (ep.espacenet.com) for European (EP), Worldwide, and World Intellectual Property Organization (WIPO) patents.

Controlled Release Product and Method for the Production Thereof (Beachpoint Holdings Inc., U.S.A.); U.S. Patent 7,615,093

This patent involves the application of a water-soluble or degradable coating to a fibrous filler material. Upon incorporation of the coated material into a solid matrix and subsequent exposure to water, the coating dissolves or degrades to create interfacial passages between the filler and matrix. Applications in the fertilizer industry are described.

Mesostructured Silica/Block Copolymer Monoliths as a Controlled Release Device and Methods of Manufacture (SBA Materials, Inc., U.S.A.); U.S. Patent 7,611,731

The invention comprises the design, synthesis, and characterization of mesostructured silica/block copolymer composite monoliths as controlled release systems. The controlled release function is based on the formation of mesostructured silica/block copolymer architectures via surfactant-templated sol-gel processing. Multi-layered or gradient monoliths are produced by layer-by-layer sol-gel processing to provide pulsed and programmed release characteristics. A simple, rapid route to prepare combinatorial compositional monolith libraries provides high-throughput synthesis and rapid screening of the release characteristics of the monoliths. Application to controlled release of molecular entities such as oral delivery of human and non-human therapeutics, coated biomedical devices, the dispersal delivery agent for agriculturally relevant molecules, various personal care and food products, biocides or pesticides, and corrosion-inhibiting agents are mentioned.

Olefin Copolymers Containing Hydrolytically Cleavable Linkages and Use Thereof in Degradable Products (SRI International, U.S.A.); U.S. Patent 7,592,408

This invention is directed to olefin copolymers composed of nonhydrolyzable monomer units and hydrolyzable monomer units, the latter resulting from copolymerization of monomers containing a linkage that is hydrolytically cleavable in the presence of aqueous base or acid. The hydrolyzable monomer units represent a significant fraction of the copolymer, such that upon hydrolysis, a substantial portion of the copolymer is degraded into low molecular weight fragments. These degradable articles include controlled release pellets, strips and tabs, agricultural film products, adhesive tape substrates, bed linens, containers, disposable absorbent articles, packaging materials, bags, labels, pillow cases, protective clothing, surgical drapes, sponges, tampon applicators, disposable syringes, temporary enclosures and siding, toys, wipes, and foamed plastic products.

Controlled Release Ceramic Particles, Compositions Thereof, Processes of Preparation, and Methods of Use (Australian Nuclear Science & Technology Organisation, Australia); U.S. Patent 7,585,521

Controlled release ceramic particles are described. Included are processes for their preparation, particle compositions, and methods of using the particles for controlled release. In one form, each of the controlled release ceramic particles has active material homogeneously dispersed throughout the particles, the active material can be released from the particles, and the active material is protected or stabilized within the particles. Applications to controlled release of fertilizers, pesticides, herbicides, insecticides, biocides, perfumes, and a wide array of pharmaceutical needs are mentioned.

Active-releasing Cyclic Siloxanes (Momentive Performance Materials Inc., U.S.A.); U.S. Patent 7,579,495

Cyclic siloxanes that contain releasable active ingredients are described. The active ingredient can be an alcohol or enolizable carbonyl-containing compound such as a ketone, aldehyde, or ester. The product siloxanes are useful in a variety of personal and household care products where slow or controlled release of an active ingredient is desired. A preferred application for controlled release of fragrances is mentioned, with applications to a wide variety of uses in personal care, household product, automotive, textile, and molding material industry products.

Cyclic Siloxane Compositions for the Release of Active Ingredients (Momentive Performance Materials, U.S.A.); U.S. Patent 7,576,170

Related to the previous patent (above).

Antimicrobial Composites, Films, Labelstocks, and Labels (Avery Dennison Corporation, U.S.A.); U.S. Patent 7,566,495

This invention relates to controlled release of chlorine dioxide gas as an antimicrobial from composites, films, labelstocks, and labels used in the food industry. The antimicrobial composites comprise a polymer mixture of at least one styrene polymer and at least one urethane polymer and an antimicrobial composition that comprises at least one metal chlorite and at least one hydrophilic material capable of reacting with the metal chlorite

when exposed to water. The composites described are useful in preparing films, labelstocks, and labels that exhibit desired antimicrobial properties by providing a controlled release of chlorine dioxide gas over an extended period of time.

Compositions for Controlled Release of Pest Control Products in Aquatic Environments (Pestalto Environmental Products, U.S.A.); U.S. Patent 7,563,453

The present invention relates to compositions and methods for the controlled release of mosquito larvacide into aquatic environments. The compositions comprise one or more pest control products in admixture with one or more water-soluble and one or more water-insoluble waxes. The compositions of this invention are particularly useful for treating columns of water in catch basins.

Flavor-Release Material and Its Use in Different Food Products (Lundberg Jan-Olof [SE]); US2009181141 (A1)

A flavor-release material comprising a potato fiber with natural or artificial cavities and a solution comprising at least one lipophilic flavoring and at least one lipophilic component, such as an oil or a fat, is disclosed. The disclosed solution is applied to the cavities to provide controlled release of flavoring. A food product comprising the flavor-release material and a method of producing the flavor-release material are disclosed.

Polysaccharide Thickener-containing Dietary Fiber Composition (Shimizu Chemical Corp [JP]); EP2087798 (A1)

This invention relates to a polysaccharide thickener-containing dietary fiber composition with functional properties that can be applied to an ingredient for foods, medicines, cosmetics, etc. Dietary fiber thickener compositions containing *Amorphophallus konjac* provide a widely applicable dietary fiber composition that may be taken to add a functional property compared with existing options. The composition can also provide a gentle elution profile of effective ingredients for such applications as medicines, nutritionals, or cosmetics.

Fast-dissolving Films and Coatings for Controlled Release of Flavors, Active Pharmaceutical Ingredients, Food Substances, and Nicotine (F. Selmin [IT], P. Blasi [IT], D. R. Worthen [US], D. Johnson [US], P. P. Deluca [US]); US2009253754 (A1)

This invention claims a fast-dissolving film for use as a platform for the delivery of material to the oral cavity that comprises a film-forming agent, a plasticizing agent, and a fast-dissolving, water-soluble agent and the methods for producing it. The invention relates to edible films and fast-dissolving edible films that can be used to provide controlled release of flavors, active pharmaceutical ingredients, foods substances, or nicotine derivatives. In one embodiment, the films are prepared by hydrating water-soluble cellulose ethers in water, emulsifying methyl salicylate with glycerin, dropping the emulsion of methyl salicylate and glycerin into the hydrated cellulosics with rapid stirring, de-gassing the resulting emulsion, depositing the de-gassed emulsion onto a substrate, and drying the de-gassed emulsion at a temperature below 40°C.

Deposition of Lipophilic Active Material in Surfactant-containing Compositions (Dow Corning [US], F. S. Galeone [BE], L. Deklippel [BE], L. A. Marteaux [BE], S. Ugazio [BE]); WO2009106318 (A2)

The present invention relates to a controlled release carrier system that can be incorporated into rinse-off application products containing at least one surfactant, such as heavy-duty liquids, rinse cycle fabric softeners, shampoos, hair conditioners, shower gels, and cleaning products, that enhances deposition of lipophilic active materials, like fragrance, fine perfumes, flavors, and other volatile compounds, onto a surface. The fragrance composition is encapsulated within a shell comprising a silicon-containing material, and the shell has a mean diameter size that is smaller than 30 μm. The surfactant composition containing the fragrance composition is washed off, and the fragrance is progressively released.

Controlled Release Particles (Akzo Nobel NV [NL], J. S. Maxim, Jr. [US], M. Crossman [US], P. M. Ferm [US]); WO2009121831 (A1)

An aqueous controlled release formulation containing formaldehyde-free water-insoluble particles having a solid core of synthetic solvent-free polymer containing a plasticizer and hydrophobic volatile liquid, such as a fragrance or perfume, and using another polymer to suspend or disperse the solid core in the aqueous formulation is described. These aqueous controlled release formulations include personal care formulations, such as washing and hair-conditioning compositions, laundry detergent compositions, and rinse conditioner compositions for fabric softening.

Fragrance Precursor (Kao Corp Sa [ES]); US2009269294 (A1)

The invention relates to a compound of the following formula (I) X-CR1R2R3, wherein -R1 is an organic moiety having 6–24 carbon atoms; -R2 is H or an organic moiety having 6–24 carbon atoms; -R3 is X or OH; and -X is a moiety of the following formula (II) or an ammonium or C1-C4 alkyl ammonium salt of the moiety of formula (II), wherein -x is 0 or 1; -y is 0 or 1; -z is 0 or 1; -m is a number from 2 to 10; -n is a number from 0 to 10; -o is a number from 0 to 10; -R4 is H or a C1-C4 alkyl group; -R5 is a C6-C22 alkyl or alkenyl group or, if n or o is at least 1, a C7-C23 acyl group; -R6 is H or R5; and -R7 is a C1-C4 alkylene group that is capable of delivering aldehyde- or ketone-type fragrance compounds, providing a long-lasting release of said fragrance compounds. This compound can be incorporated into fiber-conditioning compositions, such as hair conditioners and fabric softeners, to enhance fragrance performance. The compound provides controlled release from the substrate where it has been deposited over an extended period of time.

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Special Calcium Silicon-rich Controlled Release Fertilizer for Southern Paddy Rice and Preparation Method Thereof (Soil & Fertilizer and Resource [CN]); CN101525260 (A)

The invention discloses a special calcium silicon-rich controlled release fertilizer for southern paddy rice and a preparation method thereof. The calcium silicon-rich controlled release fertilizer is made from the following raw materials in parts by weight: 50–70 parts of a 5% special calcium silicate-coated compound fertilizer for paddy rice, 10–30 parts of a 8% special calcium silicate-coated compound fertilizer for paddy rice, 20–40 parts of a special compound fertilizer for paddy rice, and 1–3 parts of zinc sulfate. The 5% special calcium silicate-coated compound fertilizer for paddy rice and the 8% special calcium silicate-coated compound fertilizer for paddy rice, respectively, mean that the mass of calcium silicate-coated layers accounts for 5 and 8% of the total mass, respectively. The nitrogen, phosphorous, and potassium contents in the special compound fertilizer for paddy rice are 18, 8, and 20%, respectively. In the controlled release fertilizer, nutrients are regularly released, which is identical to nutrient absorption rules of southern paddy rice. Membrane materials are cheap and available, do not have degradation problems, and are environmentally friendly. The controlled release fertilizer is applied once before transplanting paddy rice; an additional fertilizer is no longer required; and the application amount of the controlled release fertilizer is reduced by 20% of that of common fertilizers, reducing the labor intensity and fertilizer fund input of farmers.

Slow Controlled Release Diatomite Fertilizer (Jilin Jiapeng Jusen Fertilizer [CN]); CN101531553 (A)

The invention relates to a slow controlled release diatomite fertilizer that is characterized by 16–20 portions of urea, 12–17 portions of diammonium phosphate, 10–15 portions of potassium chloride, and 8–12 portions of diatomite that are put in a pulverizer to be crushed and sieved by a 80-mesh sieve and then put in a granulator to be granulated by a rotary drum. Water (50–100 mL) is added slowly and uniformly to be used as a coupling agent during the granulating process. After granulation, 100–120 mL of coating material (polyvinyl alcohol) is uniformly sprayed in small amounts onto rotating fertilizer particles by a high-pressure spray gun. After coating, rosin and olefin are poured into the rotary drum based at a proportion of 1 to 2 to be melted and are made into sealant; the temperature is kept between 70 and 80°C. Finally, the coated fertilizer is poured into the rotary drum to be sealed. The invention can separate soil from fertilizer, avoids direct contact between the soil and fertilizer, and controls the release of nutrients. The slow controlled release diatomite fertilizer preserves moisture and fertility, prolongs the fertilizer effect by slow release, improves the soil, and causes no pollution to the soil.

Method of Manufacturing a Composite Based on Complexes of Controlled Stability (University of Nice Sophia Antipolis [FR], A.-M. Chaze [FR], F. Giulieri [FR], S. Ovarlez [FR]); WO2009112646 (A1)

The invention relates to a method for manufacturing a composite based on complexes of controlled stability over time, comprising, on the one hand, a fibrous inorganic matrix having tunnels and, on the other hand, one or more organic compounds incorporated into said tunnels. The invention is characterized as containing the following steps. The fibrous inorganic matrix has tunnels, and the organic compound or compounds are provided. The fibrous inorganic matrix having tunnels is mixed with the organic compound or compounds so that said organic compound or compounds are incorporated into the tunnels of the fibrous inorganic matrix. The retention of the organic compound or compounds in said tunnels and their release there from by heating the obtained mixture, at a chosen temperature for a defined time, are controlled. The invention applies in particular to preparations intended for cosmetic, pharmacological, nutri-therapeutic and agri-foodstuff, phytosanitary, petroleum, or electronic usage or paints.

Coated Pharmaceutical or Nutraceutical Preparation with Accelerated Controlled Active Substance Release (Evonik Roehm GmbH [DE], H. Ravishankar [IN], H.-U. Petereit [DE], S. Bodinge [IN]); WO2009086942 (A1)

The invention relates to pharmaceutical or nutraceutical preparations comprising a core containing a pharmaceutically or nutraceutically active substance and a (meth)acrylic copolymer-controlling layer surrounding the core. The disclosed formulations provide a release rate that increases over time.

Method for the Supply of Growth Components to Cell Cultures (Biosilta Oy [FI]); WO2009147200 (A2); EP2130906 (A1)

The invention provides a method for improving the preparation and use of growth media by the use of specific pellet formulations, especially tablets of different sizes, which contain the growth medium or parts thereof and are sterilized with the standard methods of pharmaceutical technology. Specifically, these pellet formulations are applied to control a cell culture so that the adaptation phase is shorter or the growth is controlled by the release of certain components at a certain time and in a certain concentration during the process and nutrients (e.g., nitrogen) can be packed into the cultivation vessel in amounts sufficient for high cell densities without the risk of intoxication of the organism.

Preparation of Controlled Release Long-acting Fertilizer (Jilin Academy of Agricultural [CN]); CN101481278 (A)

The invention relates to a controllable slow-release fertilizer and a preparation method thereof. Bitumen, urea, and flour are selected as raw materials for preparing coating, and the weight ratio of the bitumen, urea, and flour is 100:50–98:0.5–10. The method contains the following steps: preparing fertilizer blocks using a block molding machine or granulating with a rolling granulator; putting the bitumen into a heating container and

heating to melt the bitumen; controlling the temperature below the ignition point of the bitumen until the lowest viscosity is achieved; and adding the urea and flour to the melted bitumen and fully stirring. The preparation method of the controllable slow-release fertilizer has the advantages of being a simple process; having a low cost, low coating rate, few residual accessory ingredients, high mechanical coating strength, and randomly adjustable fertilizer release rate; and is applicable to various granular fertilizers. It can also be widely used for cultivating fruit and forest trees.

Process for Producing Chemical Fertilizer Nutrient Controlled Release Agent (Anhui Province Kingorigin Biot [CN]); CN101492320 (A)

The invention relates to a method for preparing a fertilizer nutrient loss control agent and contains the following steps: separating and screening attapulgite clay and crushing the separated and screened attapulgite clay; soaking the crushed attapulgite clay in water and acidizing the attapulgite clay with hydrochloric acid with a concentration of 0.1–5%, after microwave heating and drying; grinding the attapulgite clay; adopting pulsed pneumatic screening; obtaining powder of the attapulgite clay after screening; and adding the powder to compound materials according to the existing ratio for mixing to gain the finished product. The fertilizer nutrient loss control agent can realize volume production to promote products to emerge in market as early as possible, thereby saving the investment of farmers, improving fertilizer efficiency, improving the soil, lowering the production cost of fertilizer producers, reducing environmental protection needed, and protecting the natural environment.

Phyllosilicate Formulations for the Controlled Release of Active Substances (Bayer Technology Services GmbH [DE]); US2009170705 (A1)

Organically modified clay minerals are applied as layered seed-dressing agents for controlled release of agrochemical ingredients. The formulations comprise at least one active agrochemical ingredient for the dressing of seeds, a dispersion of biologically degradable polyester-polyurethane-polyureas, and additives. The invention relates to a method for the production of a novel controlled release seed-dressing agent formulation. Applications to cosmetics, pharmaceutical, and veterinary products are also noted.

Compositions for Protection and Release of Active Materials (Akzo Nobel NV [NL], P. M. Ferm [US], Q. W. Yuan-Huffman [US]); WO2009080695 (A1)

Compositions provide enhanced storage stability of active materials in products having aggressive media and controlled release of such active materials in use. The compositions aid in protecting sensitive ingredients in cleaning compositions, such as heavy-duty liquid compositions, while being able to deliver the majority of the sensitive ingredients in their original state during the washing and drying stages.

Water-Soluble Polymer Coating Agent, Coated Controlled Release Fertilizer, and Preparation Thereof (Shandong Kingenta Ecological E [CN], L. Wan [CN], L. Fan [CN], Q. Zheng [CN], H. Chen [CN], Y. Gao [CN]); WO2009143658 (A1)

The invention provides a water-soluble polymer coating agent, coated controlled release fertilizer containing such coating agent, and preparation method thereof. The water-soluble polymer coating agent is characterized as containing preformed polymer of alkyd resin in the form of neutralization. The coated controlled release fertilizer is composed of a fertilizer core and film outside the fertilizer core, in which such film comprises the polymer membrane containing the water-soluble polymer coating agent and optional inorganic layer containing inorganic powders outside the polymer membrane.

Water-Soluble Alkyd Resin-Sulfur Coated Controlled Release Fertilizer and Preparation Thereof (Shandong Kingenta Ecological E [CN], H. Chen [CN], L. Wan [CN], L. Fan [CN], H. Xu [CN], H. Cao [CN]); WO2009143657 (A1)

The invention provides a controlled release fertilizer coated by water-soluble alkyd resin-sulfur and preparation thereof. The controlled release fertilizer is composed of a fertilizer core and its exterior coating layer, which comprises an internal sulfur film layer, exterior polymer film containing water-soluble alkyd resin coating agent, and optional inorganic layer containing inorganic powders outside the polymer film.

Controlled Release Fertilizers Coated by Composite Layers Comprising a Water-Soluble Alkyd Resin and Wax and Their Preparations (Shandong Kingenta Ecological E [CN], Y. Gao [CN], L. Wan [CN], B. Yu [CN], Z. Li [CN], L. Fan [CN], Y. Xie [CN]); WO2009143656 (A1)

Controlled release fertilizers coated by composite layers comprising a water-soluble alkyd resin and wax and their preparations are provided. Said fertilizers comprise the fertilizer core and outer coating layers, and the coating layers comprise a wax coating layer, the surface of which is coated with a polymer coating layer comprising water-soluble alkyd resin. Optionally, the outer surface of the polymer coating layer is coated with an inorganic layer comprising inorganic powders.

Alkyd Resin Emulsion–Sulfur Multilayer-Coated Controlled Release Fertilizer and Production Thereof (Shandong Kingenta Ecological E [CN], L. Wan [CN], B. Yu [CN], L. Fan [CN], Y. Xie [CN]); WO2009143655 (A1)

An alkyd resin emulsion–sulfur multilayer-coated controlled release fertilizer contains a core material and coating layer material coated on the core material. Said coating layer material comprises a sulfur layer, polymer layer containing alkyd resin emulsion coated on the sulfur layer, and optional inorganic layer containing inorganic powder coated on the polymer coating layer.

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Controlled Release Fertilizer Coated by Alkyd Resin Emulsion Wax and Preparation Method Thereof (Shandong Kingenta Ecological E [CN], Y. Xie [CN], L. Wan [CN], L. Fan [CN], L. Li [CN], G. Li [CN], S. Xu [CN]); WO2009143654 (A1)

The invention is related to a controlled release fertilizer coated by alkyd resin emulsion wax and preparation method thereof. The coated controlled release fertilizer is composed of a fertilizer core and film outside the fertilizer core. The film contains wax film, polymer film containing alkyd resin emulsion outside the wax film, and a selectively inorganic layer containing inorganic powder outside the polymer film.

Emulsion Polymer Coating Agent, Coated Controlled Release Fertilizer and Preparation Thereof (Shandong Kingenta Ecological E [CN], L. Wan [CN], L. Fan [CN], Q. Zhang [CN], D. Chen [CN], Y. Gao [CN], H. Chen [CN]); WO2009143653 (A1)

The invention is related to an emulsion polymer coating agent, coated controlled release fertilizer that includes the coating agent, and preparation method thereof. The emulsion polymer coating agent includes prepolymer of alkyd resin in the form of neutralization. The invention is further related to a controlled release fertilizer, which is composed of a fertilizer core and film outside the fertilizer core. The film includes the polymer coat containing the emulsion polymer coating agent and a selectively inorganic layer containing inorganic powder outside the polymer coat. ■

In the News

Compiled by Steven Giannos
Industrial Editor

January 2010

Ocelus Obtains Funding for Needle-free Tech

In-PharmaTechnologist.com: January 20, 2010 – WALES, UK – Ocelus has received £500,000 from Finance Wales and the Welsh Assembly Government to fund the development of its microplant delivery system. The Cardiff firm's technology is designed to deliver high molecular weight drugs through the skin without some of the dose-reproducibility problems associated with other microneedle and poration techniques. The Ocelus approach is to inject small drug-containing particles into the skin at hundreds of sites per square centimeter. These particles then dissolve over time, steadily releasing their contents in a predictable manner.

The funding is made up of a £315,000 equity investment from Finance Wales, and £147,000 is a grant from the Welsh Assembly. Founder Andrew Kirby stated, "With this funding, we are able to continue development on our innovative system and work with leading micro-engineering, and pharmaceutical formulation companies from around the world to produce optimized prototypes for testing in human skin."

Access Pharmaceutical's Cobalamin Oral Insulin Achieves >80% Oral Bioavailability in Preclinical Models

PRNewswire: January 19, 2010 – DALLAS, TX – Access Pharmaceuticals, Inc. (OTC Bulletin Board: ACCP) has provided an update on its Cobalamin™ oral drug delivery product development programs. The proprietary Cobalamin™ technology utilizes the body's natural vitamin B_{12} oral uptake mechanism to facilitate oral absorption of pharmaceuticals by a "Trojan horse" mechanism.

Access has focused its Cobalamin™ product development program on the oral delivery of insulin and human growth hormone, two peptides that currently can only be given by injection. A new Cobalamin™-coated insulin-containing nanoparticle formulation delivered orally provided a pharmacological response (lowering of blood glucose levels in an animal model of diabetes) >80% of that achieved by insulin delivered subcutaneously. This represents a substantial oral bioavailability, indicating that this formulation has potential for clinical development and ultimate commercialization. Adaptation of this technology has provided a Cobalamin™ human growth hormone formulation that has demonstrated good efficacy, represented by more than 25% improvement in weight gain, when given orally in an established animal model. Access continues to move both products toward clinical development and plans to submit an additional patent application to protect the improvements to the technology.

"While Access continues to explore potential collaborations on multiple applications of our technology, our Cobalamin™ oral insulin product continues to be the focus of current collaborative work," said Phillip Wise, Access vice president of business development and strategy. "We continue to work with two companies testing Cobalamin™ oral insulin in multiple animal models. Meanwhile, we are pursuing options with other companies with the goal of initiating a proof-of-concept in man study."

Cobalamin™ is Access' proprietary technology based on the use of vitamin B_{12} for oral delivery of drugs that otherwise have poor oral bioavailability. It also has potential for targeted delivery of drugs to disease sites. Access is developing its Cobalamin™ technology under multiple collaborative agreements, and is in discussion with other companies regarding the application of the Cobalamin™ technology to other active drug candidates.

"While Access' focus has been on the oral delivery of peptides, the technology is sufficiently flexible to allow us to deliver a wide range of actives," commented David P. Nowotnik, Ph.D, Access senior vice president of R&D. "In addition to peptide delivery, we have received inquiries recently about the potential of this technology to deliver actives ranging from small molecules to siRNA to monoclonal antibodies. As siRNA needs to be delivered intracellularly to be effective as a therapeutic, the Cobalamin™ technology may be particularly beneficial as an intracellular delivery technology, as the demand for vitamin B_{12} increases in many disease states." Additional information on Access Pharmaceuticals is available at www.accesspharma.com.

Endo Pharmaceuticals Receives Paragraph IV Certification

PRNewswire: January 19, 2010 – CHADDS FORD, PA – Endo Pharmaceuticals (Nasdaq: ENDP) has announced that its partners, Teikoku Seiyaku Co., Ltd. and Teikoku Pharma USA, Inc. have received a Paragraph IV certification notice from Watson Laboratories, Inc. advising them of the filing of an Abbreviated New Drug Application (ANDA) for a generic version of LIDODERM (lidocaine topical patch 5%).

The company is currently reviewing the details of this notice from Watson. Endo intends to vigorously defend LIDODERM's intellectual property rights and pursue all available legal and regulatory pathways in defense of LIDODERM.

The Paragraph IV certification notice refers to U.S. Patent 5,827,529, which covers the formulation of LIDODERM, a topical patch to relieve the pain of postherpetic neuralgia launched in 1999. This patent is listed in the U.S. Food and Drug Administration's *Orange Book* and expires in October 2015.

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EKOS Corporation Announces Clinical Study for the Treatment of Pulmonary Embolism Using the EKOS EkoSonic Endovascular Device

Business Wire: January 18, 2010 – BOTHELL, WA – EKOS Corporation has announced that it is in the final planning and approval stages of a randomized clinical study for the treatment of pulmonary embolism, known as the Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) Study.

President/CEO Robert W. Hubert said, "We are pleased to announce that Dr. Nils Kucher, an internationally known expert on pulmonary embolism, University Hospital (Bern, Switzerland), will be the Principle Investigator for the study. Dr. Kucher will be joined by colleagues from the University Hospitals in Dresden, Munich and Greifswald, Germany, and several other sites." Dr. Kucher noted, "This study is, to our knowledge, the first randomized controlled trial designed to show the clinical benefit of an endovascular device to treat acute sub massive pulmonary embolism in comparison to anticoagulation therapy alone. We intend to show that treatment with low-dose, ultrasound accelerated thrombolysis [EKOS] will rapidly improve right heart failure in these patients, without introducing the risks typically associated with systemic thrombolytic therapy."

Pulmonary embolism occurs at a rate of approx. 24 per 100,000 people and accounts for up 150,000–500,000 deaths per year in the United States and Europe and effects more than 1,600,000 patients annually. Serious pulmonary emboli interfere with the heart's ability to pump blood into the lungs for oxygenation, causing enlargement of the right side of the heart and potentially causing death. Current treatments typically involve aggressive anti-coagulation, or in the most serious cases, intravenous delivery of clot-dissolving, thrombolytic agents. Anti-coagulants do not dissolve the embolism but can reduce the mortality rate. Thrombolytics actively dissolve the embolus, but are associated with an increased risk of bleeding. Neither therapy completely dissolves the embolus in all patients, leaving some patients with a chronic clot.

Hubert added, "In the ULTIMA study, 50 patients with pulmonary embolism and enlarged right hearts will be randomized to receive either standard of care anti-coagulation or Actilyse® (Boehringer Ingleheim) delivered via the EKOS EkoSonic Endovascular Device. The amount of drug necessary to dissolve a blood clot is significantly reduced when using the EKOS system because ultrasound increases the permeability of the clot while gently driving the drug into its interior. We anticipate that delivery of Actilyse® directly into the pulmonary embolism in the presence of the ultrasound generated by the EkoSonic Device will result in prompt, complete dissolution of the obstructing embolism with restoration of right heart function and a reduction in the number of patients with long-term side effects from their pulmonary embolism." Enrollment is expected to commence in Q1 2010 and be completed by Q1 2011. More information is available at www.ekoscorp.com.

Altea Therapeutics and KAI Pharmaceuticals Enter into a Preclinical and Clinical Development Agreement for the Transdermal Delivery of Certain Novel KAI Peptides

Business Wire: January 13, 2010 – ATLANTA, GA – Altea Therapeutics Corporation has entered into a partnership with KAI Pharmaceuticals, Inc., a drug discovery and development company, for the preclinical and clinical development of certain KAI proprietary peptides utilizing Altea's proprietary PassPort® transdermal delivery system.

Under the terms of the agreement, Altea and KAI will examine the transdermal delivery of certain KAI proprietary compounds using Altea's novel transdermal delivery technology, the PassPort® system. Altea has also granted KAI an option to receive a worldwide technology license for the further development and commercialization of these novel transdermal products. Should KAI exercise the option, KAI will fund all product development, manufacturing, and commercialization activities, and Altea may receive license payments, development and commercialization milestones, and royalties on product sales from KAI.

"We are pleased to enter into this agreement with KAI Pharmaceuticals," said Dr. Eric Tomlinson, Ph.D., D.Sc., president and CEO of Altea Therapeutics. "The agreement further validates the broad application of the Altea Therapeutics novel transdermal patch technology for the transdermal delivery of water-soluble compounds. While we continue to apply our transdermal technology to currently approved drugs that previously were administered by needle injection or infusion, including water-soluble proteins, carbohydrates and small molecules, this new partnership allows us to apply our technology to the new peptide drugs being developed by KAI Pharmaceuticals."

Altea Therapeutics has partnered with Amylin Pharmaceuticals, Inc. and Eli Lilly and Company to develop and commercialize a novel daily transdermal patch delivering sustained levels of exenatide (currently marketed as Byetta®). The company also has a partnership with Hospira, Inc. to develop and commercialize a transdermal patch for delivering enoxaparin sodium (currently marketed as Lovenox®) utilizing the PassPort® transdermal delivery system.

Altea Therapeutics is also in clinical development of a transdermal basal insulin patch for diabetes and a transdermal fentanyl citrate patch for pain. Additional information about Altea Therapeutics may be found at www.alteatherapeutics.com.

NexMed Announces the Ability of NexACT® Technology to Deliver Drugs Orally and with Enhanced Bioavailability

Business Wire: January 12, 2010 – SAN DIEGO, CA – NexMed, Inc. (Nasdaq: NEXM), a specialty CRO and developer of products based on NexACT® technology, has announced that pre-clinical results from its research and development group at Bio-Quant successfully demonstrated the ability of NexACT® technology to deliver an oral formulation of Taxol® (paclitaxel) and to enhance the drug's bioavailability by approx. 10-fold

through this oral administration. Taxol®, a first-line chemotherapy drug used to treat breast, lung, and ovarian cancers, is currently administered through an intravenous infusion that can take up to 24 hr to complete.

Dr. Bassam Damaj, NexMed chief executive officer stated, "The results from these proof of concept studies are exciting and support our belief that NexACT® can be successfully used to enhance oral bioavailability of a broad range of drugs, which could include our proprietary drug candidates, generic drugs and proprietary drugs owned by others who are developing second-generation formulations to provide extended patent protection with increased convenience and bioavailability. Our ability to leverage our proprietary NexACT® technology in this way is expected to provide exciting new development opportunities and will no longer restrict us to the topical delivery of dermal drugs. Additional studies are ongoing to extend the validation of the technology into other classes of oral drugs."

Sinexus Changes Name to Intersect ENT, Initiates Pivotal Study

PRNewswire: January 7, 2010 – PALO ALTO, CA – Sinexus has changed its name to Intersect ENT. Intersect's initial focus is a bioabsorbable drug-eluting stent to treat patients with chronic sinusitis, a debilitating condition that affects 37 million people each year and is more prevalent than heart disease or asthma.

"Intersect is a name that represents our mission of connecting drugs and devices to physicians and patients in need," said Lisa Earnhardt, president and CEO. "While our initial products target sinusitis, we plan to apply our novel technologies to the broad range of conditions treated by Ear, Nose, & Throat surgeons. Our goal is to provide less invasive treatment options that result in improved outcomes and reduced need for systemic drugs such as oral steroids which can lead to serious side effects."

The company also announced the initiation of its U.S. pivotal clinical study to evaluate the safety and effectiveness of its novel steroid-eluting bioabsorbable stent in patients undergoing sinus surgery. The prospective, randomized, blinded, multicenter, study is guided by thought leaders in sinusitis care.

"Two key requirements for positive outcomes after sinus surgery are maintaining a patent cavity and controlling inflammation. The clinical data from the 100 patients studied to date are encouraging," said Dr. Neil Bhattacharyya, associate professor at Harvard Medical School / Brigham & Women's Hospital. Dr. Bhattacharyya serves as co-principal investigator together with Dr. Bradley E. Marple, professor and vice chair at UT Southwestern Medical Center.

Dr. Marple added, "Patients with chronic sinusitis tend to require extensive oral steroids, which can lead to a multitude of side effects. Intersect's novel stents may alleviate the need for oral steroids and have the potential to become a powerful treatment option for sinus sufferers."

VGX Animal Health's Growth Hormone-releasing Hormone Shows Advantages Compared with Current Growth Hormone Therapies Used in Pigs

Business Wire: January 6, 2010 – THE WOODLANDS, TX – VGX Animal Health, Inc. announced that data demonstrating the effectiveness of its plasmid-based growth hormone-releasing hormone (pGHRH) technology was recently published in the peer-reviewed journal *Molecular Therapy* in a paper entitled "A Comparison of the Growth Responses Following Intramuscular GHRH Plasmid Administration Versus Daily Growth Hormone Injections in Young Pigs."

This study was conducted by VGX Animal Health scientists in conjunction with the Children's Nutrition Research Center, a cooperative venture between Baylor College of Medicine, Texas Children's Hospital, and the U.S. Department of Agriculture/ Agricultural Research Service. It was partly funded by the U.S. Department of Agriculture's National Research Initiative.

Piglets treated twice daily for 8 weeks with a currently used injectable porcine growth hormone (GH) were compared with piglets treated with a single injection of a DNA plasmid capable of expressing the naturally occurring form of porcine GHRH. The injection was followed by electroporation, which uses electrical fields to dramatically increase cellular uptake of the GHRH plasmid and expression of the GHRH.

Data generated in the study confirmed that both GH and pGHRH treatments were highly effective in increasing daily lean weight gain. Importantly, piglets in the pGHRH treatment group had the added benefit that they did not require daily hormone injections and did not experience the increases in organ weight associated with GH therapy. This study demonstrated that a single pGHRH treatment could be a viable alternative to currently used GH therapies in pigs as well as other species.

Dr. Doug Kern, VGX Animal Health vice president, business development, stated, "This is the first time a single dose of a plasmid-based growth hormone releasing hormone therapy has been directly compared to daily injections of growth hormone. Based on the results of our work, the health and growth of food animals was dramatically increased using this technology. The clear benefits to the animal and relative ease of administration warrant the assessment of this technology for application to pigs and other animals currently being administered daily injections of growth hormone."

Kevin Rassas, VGX Animal Health president, stated, "The growth responses observed in piglets with administration of the pGHRH plasmid technology, i.e. without direct administration of GH, are a significant improvement over the daily use of growth hormone or growth hormone analogs. These results suggest that this new application could be an important complement to our LifeTide® product, which is also based on VGX's pGHRH technology. We continue market development

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efforts for LifeTide® SW 5 in Australia and efforts to secure regulatory approval for LifeTide® SW 5 in new markets."

VGX Animal Health's GHRH product for pigs, LifeTide® SW 5, is administered as a once-in-a-lifetime treatment for use in sows of breeding age. Licensing studies completed in Australia demonstrated a significant decrease in perinatal mortality and morbidity, resulting in an increase in sow productivity and the number of pigs weaned per sow. LifeTide® SW 5 is the world's first therapeutic plasmid delivered by electroporation to be approved for use in food animals. The product was approved in Australia in January 2008 by the Australian Pesticides and Veterinary Medicines Authority.

CyDex Pharmaceuticals Receives a Key U.S. Patent for Composition of Matter and Process of Manufacturing High-Purity Captisol®

Business Wire: January 5, 2010 – LENEXA, KS – CyDex Pharmaceuticals Inc., a specialty pharmaceutical company, has announced that the U.S. Patent and Trademark Office has issued a patent to CyDex entitled "Sulfoalkyl Ether Cyclodextrin Compositions." This patent, along with other previously issued technology patents, will provide broad protection for CyDex's Captisol technology until 2029. The most recent of these previously issued patents, for a new Captisol that flows better, dissolves faster, and packs more densely than previous morphologies, was announced on December 9, 2009.

The latest patent announced (U.S. Patent 7,635,773) covers a manufacturing process for producing ultra high-purity modified cyclodextrins, specifically the β-cyclodextrin sulfobutyl ether sodium salt product known as Captisol. Captisol is CyDex's proven enabling drug delivery technology that aids in the solubilization, stabilization, and taste masking of active pharmaceutical ingredients.

"Receiving this new patent is an important achievement as we continue to license Captisol technology and develop our own products that target unmet needs in hospital intravenous therapy," said Dr. Theron Odlaug, president and chief executive officer of CyDex Pharmaceuticals. "High-purity Captisol removes many impurities and degradants so that the composition can be used to increase the stability of highly sensitive active pharmaceutical ingredients. Together with the morphology patent we received earlier this month, this patent ultimately provides broader protection for our clients using Captisol and provides them with critical life-cycle management for their products."

Captisol is manufactured using a validated, patent-protected process and conforms to USP 1078 on Good Manufacturing Practices for Bulk Pharmaceutical Excipients.

Dicerna Signs Research Collaboration and License Agreement for Drug Delivery Systems and Dicer Substrate siRNA (DsiRNA) Pharmaceuticals with Kyowa Hakko Kirin

Business Wire: January 4, 2010 – WATERTOWN, MA – Dicerna Pharmaceuticals, Inc., a second-generation RNA interference (RNAi) company developing novel therapeutics utilizing its proprietary Dicer Substrate Technology™ and Dicer Substrate siRNA (DsiRNA) molecules, and Kyowa Hakko Kirin Co., Ltd. (TSE: 4151), one of Japan's leading biopharmaceutical companies, announced that the two companies have entered into a research collaboration and license agreement for the research, development, and commercialization of drug delivery systems and DsiRNA pharmaceuticals for therapeutic targets in oncology.

"We are very pleased to enter into this exciting collaboration with Kyowa Hakko Kirin," said James C. Jenson, Ph.D., chief executive officer and co-founder of Dicerna. "This partnership is a further validation of Dicerna's proprietary Dicer Substrate Technology™ platform and our unique ability to generate a greater number of more potent molecules. This collaboration provides us with the opportunity to develop novel Dicer Substrate siRNA therapies and related drug delivery systems while working with an innovative biopharmaceutical partner."

Under the terms of the collaboration, Dicerna will receive $4 million in upfront cash payments, including research funding, and up to $120 million in additional research funding and development and commercial milestones for exclusive rights to one target in the field of oncology. According to the progress of the research collaboration, Kyowa Hakko Kirin and Dicerna may expand the scope of the collaboration by adding up to approx. 10 targets under similar terms and may broaden the therapeutic focus of the partnership. Dicerna is entitled to royalty payments on sales from products for these targets. Dicerna also has an option to equally co-promote and profit-share (50:50) in the United States for the initial target.

"Dicer Substrate Technology™ is a highly promising approach to provide innovative RNAi-based therapeutics. Combining with our drug delivery system will enable us to jointly offer new treatments for cancer as well as other diseases," said Etsuo Ohshima, Ph.D., managing officer and vice president of the Research Division at Kyowa Hakko Kirin. "This collaboration… reinforce[s] the possibility of DsiRNA-based medicines by means of specific delivery to tumors or certain tissues. We believe that this endeavor to modulate intracellular targets can be complementary to our own antibody-based approach featuring POTELLIGENT® technology to cell surface targets. Dicerna will be an important partner for Kyowa Hakko Kirin to open an opportunity of new medications for patients."

"We look forward to a very productive partnership with our colleagues at Kyowa Hakko Kirin, a company with an interest in RNA interference therapeutics," said Martin D. Williams, chief business officer at Dicerna. "We have been impressed by Kyowa

Hakko Kirin's experience with gene silencing and drug delivery systems. In Kyowa Hakko Kirin, we believe we have found a partner who shares our vision of the importance of bringing this important new therapeutic category to market, and commitment to develop DsiRNA-based medicines for the benefit of patients."

December 2009

Alnylam and Collaborators at MIT Report New Pre-clinical Research on Systemic Delivery of RNAi Therapeutics

Business Wire: December 29, 2009 – CAMBRIDGE, MA – Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, and collaborators from the David H. Koch Institute for Integrative Research at the Massachusetts Institute of Technology (MIT) have announced the publication of new data in the journal *Proceedings of the National Academy of Sciences* describing further advancements in discovery and development of novel "lipidoid" formulations for the systemic delivery of RNAi therapeutics. Lipidoids are lipid-like materials that can be used for the delivery of RNAi therapeutics and were originally described by Alnylam and MIT collaborators (Akinc et al., *Nature Biotechnology*, 2008; 26:561-569). In particular, the new research findings demonstrate the discovery of new lipidoid materials that facilitate significantly improved *in vivo* potency for RNAi therapeutics.

"We are very encouraged with the substantial progress we and our collaborators have made with lipid nanoparticles (LNPs) based on novel lipid-like materials such as lipidoids," said Victor Kotelianski, M.D., Ph.D., D.Sc., senior vice president, Distinguished Alnylam Fellow. "To our knowledge, these new LNP formulations facilitate endogenous liver gene silencing at doses that are orders-of-magnitude lower than those required by previously described siRNA delivery approaches, thereby setting a new standard in potency for the systemic delivery of RNAi therapeutics. In addition, the current study is the first to report on the simultaneous and highly specific RNAi-mediated silencing of as many as five liver targets *in vivo*, serving as proof of principle that multiple genes involved in similar or divergent biological pathways can be silenced with a single administration of a single drug product. From a therapeutic standpoint, this could enable novel pharmaceutical strategies, where silencing of multiple targets could achieve an enhanced level of efficacy."

The new pre-clinical data describe a formulation based on a lipidoid known as "C12-200" that was shown to

- Enable gene silencing *in vivo* in rodents at doses below 0.01 mg/kg.
- Demonstrate complete, rapid, and durable gene silencing in rodents as soon as 24 hr with protein levels returning to baseline within 20 to 35 days.
- Specifically inhibit expression of as many as five target genes simultaneously after a single injection of an LNP formulation in rodents.
- Demonstrate potent and selective silencing of the clinically relevant gene transthyretin (TTR) at doses as low as 0.03 mg/kg in non-human primates.

"We are excited by the delivery performance of these new formulations," said Daniel Anderson, Ph.D. of the David H. Koch Institute for Integrative Cancer Research at MIT. "This work demonstrates that doses measured in micrograms per kilogram can provide potent gene silencing with RNAi in several species including primates. This greatly improved efficacy allows us to dramatically decrease the dose levels of LNPs, thereby widening the therapeutic index, and also opens the door to formulations that can simultaneously inhibit multiple genes or pathways."

Lipidoid formulations represent one of several approaches Alnylam is pursuing for systemic delivery of RNAi therapeutics. Additional approaches include other lipid nanoparticle formulations, mimetic lipoprotein particles (MLPs), siRNA conjugation strategies, and single-stranded RNAi, among others. Alnylam is currently enrolling patients in a Phase I clinical program with its systemic RNAi therapeutic ALN-VSP for the treatment of liver cancers. In addition, Alnylam intends to initiate a Phase I trial in the first half of 2010 for an additional systemic RNAi therapeutic, ALN-TTR for the treatment of TTR-mediated amyloidosis. ALN-VSP and ALN-TTR both utilize a first-generation lipid nanoparticle formulation known as stable nucleic acid-lipid particles (SNALP) that was developed in collaboration with Tekmira Pharmaceuticals Corp.

Sanofi-aventis to Acquire Chattem Inc., Creating a Strong U.S. Consumer Healthcare Platform

PRNewswire-FirstCall: December 21, 2009 – PARIS, FRANCE, and CHATTANOOGA, TN – Sanofi-aventis (EURONEXT: SAN and NYSE: SNY) and Chattem, Inc. (Nasdaq: CHTT) announced that they have entered into a definitive agreement under which Sanofi-aventis is to acquire 100% of the outstanding shares of Chattem in a cash tender offer for $93.50 per share or approx. $1.9 billion. The transaction will create the world's fifth-largest consumer healthcare company measured by product revenues by combining Chattem's position as a leading U.S. consumer healthcare company with Sanofi-aventis' strong international presence in the sector.

Over-the-counter (OTC) and consumer brands are core growth platforms identified in Sanofi-aventis' broader strategy for achieving sustainable growth. Although the group generated around €1.4 billion worldwide in OTC sales in 2009, it has thus far not been directly present in the United States.

Chattem is approx. 130 years old and is a leading manufacturer and marketer of branded consumer healthcare products, toiletries, and dietary supplements across niche market segments in the United States. Chattem has regularly demonstrated its ability to sustain regular growth, both in terms of sales and profits, through the development of its own brands and the successful integration of acquired products. Chattem's well-known brands include Gold Bond®, Icy Hot®, ACT®, Cortizone-10®, Selsun Blue®, and Unisom®.

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Sanofi-aventis has also announced that it will seek to convert its antihistamine brand known as Allegra® (fexofenadine HCl) in the United States from a prescription medicine to an OTC product. Allegra® is a well-recognized brand name with both physicians and consumers. Upon Allegra®'s conversion, Chattem will assume responsibility for the Allegra® brand as part of becoming the platform for Sanofi-aventis' U.S. OTC and consumer healthcare business.

"The acquisition of Chattem will be a significant milestone in Sanofi-aventis' transformation strategy and will provide us with the ideal platform in the U.S. consumer healthcare market, which represents 25 percent of the current worldwide opportunity," said Christopher A. Viehbacher, chief executive officer of Sanofi-aventis. "In addition, we believe our ability to convert prescription medicines to OTC products will be enhanced by Chattem's leading sales, marketing and distribution channels. We have great respect for Chattem's world-class management team, which has an excellent track record of sales and earnings growth based on building strong brands. With the potential access to switch products such as Allegra®, I believe this team will take Chattem to even higher levels."

"This transaction offers immediate and significant value for Chattem's shareholders and important benefits to our employees, customers and community," said Zan Guerry, chair and chief executive officer of Chattem. "I am excited to work with the Sanofi-aventis team to capture the significant growth opportunities this combination creates, as highlighted by the planned launch of Allegra®. Chattem will form the base of a new consumer healthcare business in the United States for Sanofi-aventis, and the headquarters, manufacturing and leadership team will continue to be based in Chattanooga."

For additional information on the transaction, please visit http://multivu.prnewswire.com/mnr/sanofi-aventis_chattem/41630

Meta-analysis of Independent Research Supports Potential for Oral Salmon Calcitonin Using Emisphere's Eligen® Technology as a Therapeutic Option for Persistent Musculoskeletal Pain

Business Wire: December 21, 2009 – CEDAR KNOLLS, NJ – Emisphere Technologies, Inc. (OTC BB: EMIS) has announced the publication of a meta-analysis in the December 2009 edition of *Rheumatology Reports* that examines independent evidence of the analgesic action of the hormone calcitonin. This publication restates the potential of calcitonin in filling a significant unmet need for alternative treatments for persistent musculoskeletal pain.

Oral salmon calcitonin, which uses the proprietary absorption-enhancing Eligen® drug delivery technology, is being studied in osteoarthritis and osteoporosis by Novartis Pharma AG and Nordic Bioscience. Scientists from Nordic Bioscience were involved in the preparation of this meta-analysis.

Non-malignant musculoskeletal pain is the most common clinical symptom that causes patients to seek medical attention and is a major cause of disability in the world. Musculoskeletal pain can arise from a variety of common conditions, including osteoarthritis, rheumatoid arthritis, osteoporosis, surgery, low back pain, and bone fracture.

The meta-analysis, conducted by researchers at the Center for Sensory-Motor Interaction in the Department of Health Science and Technology at Aalborg University in Denmark, examined independent pre-clinical and clinical studies spanning nearly 45 years of the possible intrinsic analgesic properties of calcitonin, with special focus on the challenges in the musculoskeletal system. The authors concluded that well-designed clinical trials should be conducted to further validate evidence of calcitonin's analgesic action and its promising potential role in the management of musculoskeletal pain.

The effects of calcitonin on clinical pain conditions have received increasing attention in recent decades, although a consensus on the mechanism of action and potential indications has not been reached. The analgesic activity of oral salmon calcitonin has been shown in several controlled prospective double-blind studies; in addition to pain management in osteoporosis, calcitonin has shown analgesic action in painful conditions such as phantom limb pain, diabetic neuropathy, complex regional pain syndrome, adhesive capsulitis, rheumatoid arthritis, vertebral crush fractures, spondylitis, tumor metastasis, cancer pain, migraine, Paget's disease of bone, as well as post-operative pain.

"An ideal treatment with an optimal efficacy, safety and convenience profile is not available for the musculoskeletal pain associated with such conditions as osteoporosis and osteoarthritis. This review of the literature highlights the clear unmet medical need that could be addressed by Emisphere's oral salmon calcitonin product," said Michael V. Novinski, president and chief executive officer, Emisphere Technologies.

Exclusive Licensing Agreement Concerning Gene Therapy with The University of Tokyo and TODAI TLO Ltd. and Re-granting Agreement with NOF Corporation Ltd.

In-PharmaTechnologist.com: December 21, 2009 – NanoCarrier Co., Ltd. – NanoCarrier has announced that NanoCarrier and The University of Tokyo and its TLO (TODAI TLO) have signed a licensing agreement for their gene therapy patents, of which TODAI TLO has the right to grant license of use. In the agreement TODAI TLO grants NanoCarrier the right of exclusive use, with the sub-licensing right of the patents in Japan as well as foreign countries. Based on this agreement, NanoCarrier has granted to NOF Corporation the exclusive license limited to the gene therapy area, with sub-licensing rights. This agreement is constituted by the technology of polymeric micelle carriers made of cationic polyamino acids invented by Prof. K. Kataoka of The University of Tokyo and his group. The technology featured polymeric micelle carriers and negatively charged genes that form macromolecular ionic complexes of nano-size particles. NanoCarrier can add the area of gene therapy with this agreement to our patent lineup and receive "sub-licensing fees," "running royalties," and "sub-sub-licensing fees" from NOF Corporation, whom NanoCarrier re-granted the

license for use of "Gene Therapy using genes that express functional proteins."

NOF is pursuing development and commercialization of materials and prescriptions for drug delivery and searching novel technologies applied to gene therapy. Gene therapy cells synthesize RNAs and functional proteins based on the genetic codes of DNAs when expression vectors with DNAs are transferred inside cells. Gene therapy applies this system for the treatment of various diseases. Detoxified viruses are used as vectors, but the novel method to transfer genes inside cells is desired.

Flexible Artificial Blood Cells Could Improve Drug Delivery Says U.S. Group

In-PharmaTechnologist.com: December 17, 2009 – Santa Barbara, CA – Artificial red blood cells (RBC) that mimic "biologically optimized" characteristics could improve nanotech drug delivery, according to a group of U.S. scientists. The team from the University of California modified spherical poly-lactic-*co*-glycolic acid (PLGA) particles using an alcohol treatment until they formed the classic "dimpled" RBC shape. This was then used as a mold on which multiple layers of cross-linked proteins were built up, creating, when the PLGA core was dissolved, a flexible shell capable of passing through tubes the size of blood capillaries.

Lead researcher Samir Mitragotri said that while current strategies focused on creating nano-carriers have advanced drug delivery, the carriers themselves "lack the sophistication exhibited by innate biological entities." Prof. Mitragotri explained that, in contrast, RBCs are "highly specialized entities with unique shape, size, mechanical flexibility, and material composition, all of which are optimized for extraordinary biological performance."

The work is detailed in a paper entitled "Red Blood Cell-mimicking Synthetic Biomaterial Particles," that has been published in the *Proceedings of the National Academy of Sciences*. In addition, although work on use of the artificial RBCs for drug delivery is at a relatively early stage, the team has already used them to transmit iron-oxide nanoparticles, according to a report in an article in the MIT *Technology Review*. Prof. Mitragotri and his team are now looking at how the artificial RBCs perform in animal models to fully assess their potential in drug delivery.

SRI International Receives U.S. Patent for Needle-free Transmucosal Drug Delivery System

PRNewswire: December 15, 2009 – MENLO PARK, CA – SRI International, an independent nonprofit research and development organization, has announced the award of U.S. Patent 7,592,021 for a new bioadhesive drug delivery system that enables enhanced release of drugs through the human body's mucous membranes. This needle-free option uses gels for drug delivery and allows for a much longer release time compared to alternatives such as sprays or liquids.

Transmucosal delivery is an effective means to introduce drugs across the mucous membrane to the systemic circulation, avoiding the gastrointestinal tract and "first pass liver metabolism," which can result in only a small proportion of a drug reaching the desired targets in the body. The ease of transmucosal administration, by nebulizers or bottles, for example, often improves patient compliance compared to other forms of drug delivery. The sustained and enhanced release of therapeutic and preventive treatments enabled by SRI's bioadhesive drug delivery invention can significantly improve effectiveness and outcomes.

"This needle-free system can be used for drug delivery in any environment, even in locations where sterile medical supplies are unavailable," said Gita Shankar, Ph.D., director of formulations R&D at SRI and an inventor of the system. "Offering this option to patients can increase access to safe, effective medical care for a wide variety of conditions."

SRI's patented formulation is a two-component polymeric solution: one is responsive to pH and the other to temperature. Upon mixing and application to the physiological site, the two components form an adhesive gel that attaches to the mucosa, creating a platform for drug release. Choice of application site varies depending on a variety of factors, including the duration and frequency of drug administration and the desirability of controlled release. SRI's transmucosal drug delivery system is equally well suited for both systemic conditions that affect the whole body and localized conditions that affect specific parts of the body.

The mucous membrane of the nasal cavity is most frequently used for delivery of antigens and medications against localized infections. Because mucous membranes respond strongly to foreign matter and can offer a hospitable environment for pathogens and antigens, they are ideally suited for the introduction of vaccines, where both systemic and local immune responses are desired. Most pediatric vaccines are injections, which can be painful to children and difficult to administer safely in poorer regions of the world. SRI's needle-free technology can be used to safely deliver vaccines nasally, including those for pediatric use. The system can also be used to administer contraceptive formulations or to provide topical microbicides that protect against sexually transmitted diseases, such as HIV and genital herpes.

The novel bioadhesive drug delivery system was developed as part of an SRI project funded in part under a National Institutes of Health grant to develop a nasal formulation for anthrax antigens suitable for mass immunization in the event of a bioterrorism emergency. Other applications being developed include use of the drug delivery system to deliver therapeutics that protect against chemical warfare agents.

The project described was supported by grant 1 R03 AI059234 from the National Institute of Allergy and Infectious Diseases, a division of the National Institutes of Health.

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Yissum Presents New Antiviral Hand Sanitizer That Completely Inactivates Swine Flu Virus

Business Wire: December 14, 2009 – JERUSALEM, ISRAEL – Yissum Research Development Company Ltd., the technology transfer arm of The Hebrew University of Jerusalem, presents EtoClean™, a new antiviral hand sanitizer that has been found to be highly effective against the swine flu virus. The novel product was invented by Prof. Elka Touitou from the School of Pharmacy, Faculty of Medicine, at The Hebrew University of Jerusalem, and is being developed by Novel Therapeutic Technologies (NTT), a spin-off company of Yissum.

Results of tests conducted on clinically isolated H1N1 virus from patients, the actual pandemic strain of the virus, demonstrate that the innovative composition completely inactivates the swine flu virus within 15 sec of exposure. The tests were carried out according to the American Society for Testing and Materials protocol in an FDA-certified laboratory in the United States.

"EtoClean™ appears to completely inactivate the swine flu virus almost immediately, while most hand sanitizers available on the market today were not tested specifically for swine flu," said Yaacov Michlin, president & CEO of Yissum. "Yissum and NTT are currently seeking a strategic partner for the further development of this product, which has clear potential to provide a solution for the spreading of viral infectious diseases."

The new sanitizer exhibits microbicidal and antiviral properties that are effective for sanitizing a variety of surfaces, foods, and skin. As such, it is being developed by NTT as a full range of products for different sanitizing uses in various pharmaceutical forms. Furthermore, the novel sanitizer compositions contain GRAS (generally regarded as safe) ingredients, which are safe for use and environmentally friendly. The sanitizer does not dry the skin, allowing for frequent use of the product, and leaves a pleasant feeling after application. In addition, the product also inactivates many non-enveloped viruses, such as hepatitis and noroviruses, which are not susceptible to regular alcohol-based sanitizers.

GSK and Intercell Form Strategic Alliance to Develop and Commercialize Innovative Needle-free Patch-based Vaccines

December 11, 2009 – LONDON, UK, and VIENNA, AUSTRIA – GlaxoSmithKline Biologicals SA (GSK) and Intercell have announced an agreement to form a strategic alliance to accelerate the development and commercialization of needle-free, patch-based vaccines. The agreement will include Intercell's candidate vaccine for travellers' diarrhea (TD) and an investigational single-application pandemic influenza vaccine, as well as the use of the patch technology for other vaccines in GSK's portfolio.

Under the terms of the agreement, GSK will make an up-front cash contribution of €33.6 (£30) million, in addition to an equity investment of up to €84 (£75) million through a staggered shareholding purchase option of up to 5 % in Intercell. Included in the agreement are Intercell's investigational TD vaccine, currently in Phase III, and an investigational single-application pandemic influenza vaccine in Phase II, as well as other potential future patch vaccines.

"This novel technology has real potential to change the way vaccines are delivered in the future. GSK has an extensive portfolio of vaccines and we believe needle-free vaccination could offer benefits such as simplified administration and increased compliance." said Jean Stephenne, president of GSK Biologicals. "This agreement demonstrates how, as an integral part of our R&D programme, we not only look at new vaccines but also at alternative approaches to oral and intramuscular administration."

"This new partnership is combining the forces of Intercell's innovative needle-free vaccination programme and technologies with a vaccine leader's strength in development and commercialisation. In addition, we can pursue our business strategy of creating significant shareholder value as an independent company whilst continuing to develop one of the most innovative product pipelines in the industry," said Gerd Zettlmeissl, chief executive officer of Intercell.

Each year, approx. 20 million international travelers develop TD while visiting endemic areas in Asia, Africa, and South America. Currently, there is no vaccine available to address this medical need. GSK and Intercell will collaborate on the TD vaccine patch, currently in Phase III, to commercialize this vaccine once it has gained regulatory approval. The agreement will also include a collaboration between the two companies to further develop and co-market an innovative pandemic influenza vaccination approach.

Merrimack Buys Drug Delivery Business Hermes

PRWEB: December 7, 2009 – CAMBRIDGE, MA – Merrimack Pharmaceuticals, Inc. has announced that it has acquired Hermes Biosciences, Inc., a private biotechnology company based in South San Francisco, CA. Hermes specializes in targeted drug delivery technologies for therapeutic and other biomedical applications using lipidic nano-carriers and antibodies as targeting agents.

"The acquisition of Hermes, is part of Merrimack's strategy to apply our systems biology approach to drug discovery and development to an expanding array of disease-fighting targets and technologies," said Robert Mulroy, president and CEO of Merrimack Pharmaceuticals." "We believe that coupling Merrimack's approach of identifying critical targets through systems analysis with our innovative drug delivery technologies creates great potential to generate truly novel therapies that can provide significant benefit to cancer patients," said Dr. John Park, president, CEO, and a founder of Hermes.

Merrimack's proprietary Network Biology platform applies techniques from the fields of computational modeling, high-throughput biology, and engineering to understand cell system

dynamics and develop therapeutics to address cell malfunctions in a disease state. The first candidates to be developed out of this approach are MM-121, a first-in-class ErbB3 antagonist, and MM-111, a bispecific antibody targeting ErbB2 and ErbB3. Both candidates are in Phase I development and are expected to enter Phase II in 2010.

Tris Pharma Announces Two NDA Approvals from the FDA, Including a Pioneering, First-Ever 24-hr Liquid Sustained-Release Product

PRNewswire: December 7, 2009 – SOUTH BRUNSWICK, NJ – Tris Pharma, a specialty pharmaceutical company that develops innovative drug delivery technologies, announced that the U.S. FDA has approved its first two New Drug Applications (NDAs) based on its proprietary OralXR+™ platform technology, including the first-ever 24-hr liquid sustained-release product.

OralXR+™ is a portfolio of dosage forms based on a patent-pending sustained-release particle-driven technology. Tris creates extremely fine, taste-masked, sustained-release particles that can deliver drug over time. The particles are coated with a highly flexile, insoluble, water-based polymer, resulting in highly durable particles that can be used in an array of dosage forms, including liquid suspensions, ODT, chewable tablets, and film strips, as well as traditional tablets or capsules.

The NDA approvals received were for once-daily Clonidine ER suspension and once-daily Clonidine ER tablets in two different strengths. Clonidine, a heavily prescribed medication is a direct-acting α-2 adrenergic agonist that has been prescribed historically as an antihypertensive agent. Until Tris Pharma's approval, there were no once-daily oral Clonidine products available.

"The suspension represents a true leap forward for drug delivery in that it is the first-ever FDA approved 24 hour sustained release liquid formulation," said Ketan Mehta, CEO and president of Tris Pharma. "These two NDAs further validate Tris' pioneering work in the field of liquid sustained release. This is a testament to the people of Tris Pharma's relentless work and dedicated efforts to make this a reality."

Liquid sustained-release stands apart from the traditional ER solid dose in that it allows physicians a limitless number of dose options, since the dose can be customized through titration. It also allows patients who have difficulty swallowing pills, typically young children and the elderly, to realize the convenience and compliance benefits of drug delivery. "This will be particularly valuable as the technology is leveraged in the development of CNS, pain, and other important therapeutic dose-ranging compounds," stated Dr. Yu-Hsing Tu, head of R&D at Tris. Tris Pharma has a robust pipeline of more than 20 extended-release products in different therapeutic categories currently in development.

Tris Pharma is a privately owned, product-focused, specialty pharmaceutical company engaged in the research and development of innovative drug delivery technologies. Through its OralXR+ platform, Tris has pioneered the delivery of sustained release in liquid, chewable/ODT, and strip dosage forms, so patients do not have to swallow a pill. Tris' Nobuse platform provides abuse-deterrence for opioids and other abuse-prone drugs. The company has more than 20 Rx and OTC products in development with pharmaceutical partners. Tris' R&D and manufacturing facilities are located in Monmouth Junction, NJ. For more information, visit www.trispharma.com.

Diurnal Receives Investment to Develop Delivery Tech

In-PharmaTechnologist.com: December 7, 2009 – CARDIFF, UK – Diurnal has received a £600,000 ($982,000) investment for further development of products using its drug delivery technology, which uses delayed and sustained release to mimic the body's circadian rhythm. The delivery technology has potential to treat patients with deficiencies in steroid or thyroid hormones, testosterone, and related conditions by regulating metabolism, growth, development, and puberty.

Diurnal is working with Penn Pharmaceuticals Simbec Research to develop Chroncort, a treatment for adrenal insufficiency and the company's lead candidate. Using the funding, Diurnal is aiming to complete Phase I trials in the first half of 2010. Fusion IP contributed £300,000 of the investment, with Finance Wales putting forward the rest.

Terapio Secures $5 million in Series A Financing from Santé Ventures

Business Wire: December 1, 2009 – AUSTIN, TX – Terapio Corporation, a development stage biotechnology company based in Austin, Texas, today announced it has secured $5 million in equity financing from Santé Ventures.

Terapio is developing a pipeline of therapeutic applications based on the unique properties of RLIP76, a transport protein that helps move large molecules across the cell membrane. The first application of Terapio's technology is as a radiation countermeasure, which has been demonstrated by the company in animal studies in which the protein significantly increased overall survival of mice exposed to otherwise lethal doses of radiation, even when the protein was administered orally after radiation exposure. RLIP76 helps mitigate the harmful effects of ionizing radiation and chemical toxins by providing cells with an increased ability to tolerate the oxidative stresses associated with reactive glutathione S-conjugates. A second application is in drug delivery, exploiting the protein's remarkable ability to promote its own uptake by cells when presented in the outer layer of a liposome. The company has demonstrated systemic absorption and delivery of both the protein and liposomal contents with oral administration, including the ability to deliver genetic material across the blood-brain barrier.

Terapio was founded in 2005 based on intellectual property under exclusive license from the University of Texas at Arlington generated from research by Dr. Sanjay Awasthi. The Series A financing

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from Santé Ventures is in addition to $3.2 million Terapio has previously received from the Texas Emerging Technology Fund, the National Institutes of Health, and angel investors. Proceeds from this financing will be used to continue preclinical development of the radiation countermeasure and drug delivery applications and to prepare an Investigational New Drug (IND) application with the FDA to begin human clinical trials.

"We have been following this company's scientific progress since inception," said Santé Ventures Managing Director Kevin Lalande. "While keenly aware of the challenging fundraising environment for early-stage biopharma companies, we nevertheless found in Terapio a compelling combination of platform technology with applications in multiple large target markets and relatively modest capital requirements."

Terapio has been working in the offices of Santé Ventures over the past year and is also a member company of the Austin Technology Incubator. "A major benefit of working at Santé has been the interaction with the partners and other professionals," said Terapio CEO and BioAustin Chair Dr. Curt Bilby. "In addition to their domain knowledge and business acumen, Santé's network has given us access to expertise that we would never have had otherwise and has helped us attract and build a very experienced team; most recently Dr. Vadim Klyushnichenko joined us to lead our drug development effort and Dr. Charles Dowding to spearhead our preclinical programs. With the support of Santé, the capital raised and our team, we have the resources to continue our progress commercializing biologics for both government and commercial applications."

November 2009

Merck KGaA Plans €150-million Clinical R&D Centre in China

In-PharmaTechnologist.com: November 24, 2009 – Merck KGaA cites China's growing drug market as the key driver for the new €150-million ($224-million) clinical R&D hub it plans to set up in Beijing. The facility, which will be operated by Merck Serono, will manage the German drug maker's clinical trial operations in the country and, according to spokesperson Gangolf Schrimpf, will build on its existing presence. Dr, Schrimpf stated that "Merck is keen to further develop in-house clinical research capacity in emerging markets," adding that the firm already has 50 dedicated R&D staff in China. Schrimpf went on to say, however, that, despite the new in-house capacity the center will provide, "co-operation with local contract research organisations [CROs] is not out of the question," explaining that Merck is currently involved in six such partnerships in the country. He added that the center will house biomarker, pharmacogenomics, and bioanalytics and is primarily designed to serve the growing Asian market, which was a key driver for the investment.

Schrimpf also stressed the center's role in Merck's wider R&D network, which includes units in Germany, Switzerland, and the United States, citing the recent FLEX Erbitux study as an example of one that included patients from both Asia and Europe. Merck Serono plans to access China's R&D pool to staff the new facility, according to R&D Executive Vice President Bernhard Kirschbaum, who said the firm's efforts to recruit locally will benefit both its operations in China and its global research capacity. In all, Merck expects to create 200 new research jobs at the facility over the next four years.

Development of Sustained-Release Docetaxel

November 19, 2009 – NanoCarrier Co., Ltd. – A new DDS formulation NanoCarrier Co., Ltd. has successfully developed a new nanomicellar formulation of sustained-released docetaxel. The docetaxel-incorporating nanomicellar formulation can adequately control the release rate of docetaxel from micellar nanoparticles and possibly reduce the adverse effects of docetaxel, such as gastrointestinal toxicities, edema, etc., while obtaining its efficacy.

In experimental studies using human cancer models in mice, docetaxel-incorporating micelle showed antitumor effects that were equal to or better than conventional docetaxel, while there was much less weight loss observed. Docetaxel-incorporating nanomicelle has a different structure than paclitaxel-incorporating nanomicelle (NK105), which also belongs to the taxane family. We are developing docetaxel-incorporating micelle as a succeeding candidate of NK105, as there is a six-year gap in the development schedule between this new drug and NK105. NanoCarrier will perform additional studies for docetaxel-incorporating micelle and move forward with granting licenses to pharmaceutical companies.

Docetaxel is an anticancer agent that has been marketed by Sanofi-aventis under the brand name of Taxotere® since 1994. This agent is widely used for the treatment of breast cancer, non–small cell lung, gastric, uterine, ovarian, and prostate cancers. Sales of docetaxel are still strong, with approx. 300 billion yen in the global market. On the other hand, use of this agent is known to produce the following adverse effects: edema, bone-marrow suppression, gastrointestinal disorders (nausea and vomiting), alopecia, hepatic dysfunction, hypersensitivity reaction, and general fatigue. We believe docetaxel-incorporating micelle can relieve patients of these adverse effects and help them improve the quality of life of cancer patients.

Cafosa Launches Gum Delivery Excipient

In-PharmaTechnologist.com: November 17, 2009 – Spanish ingredient supplier Cafosa has launched a new directly compressible pharmaceutical excipient for medicated chewing gums that, it claims, can boost patient compliance.

The firm said that the excipient, known as "Health in Gum," provides drug makers with an innovative oral delivery system that can be added to drug formulations without specialized processing equipment. Company spokesperson Marta Carbo stated that "There is a long list of APIs that can be combined with Health in Gum, covering several therapeutic areas, including analgesia, allergy, digestive as well as cough and cold medications." Carbo added that "Medicated chewing gum has

been considered a valid drug delivery system for years, but could never be developed to a greater extent…because it required a considerable investment in specific equipment and technology in order to manufacture chewing gum with ordinary gum bases."

She went on to say that Cafosa is optimistic about demand for the new excipient, explaining that it is "already present in some commercially available products and we currently have several promising projects running in trial phase." "We expect a growing demand for the excipient in the coming years. Moreover, Cafosa has always been an innovative company, so we will maintain our constant efforts in developing new products and applications for chewing gum in pharmaceuticals.

GSK and Nabi Announce Agreement for NicVAX®, a Vaccine for Nicotine Addiction

GlobeNewswire: November 16, 2009 – LONDON, UK, and ROCKVILLE, MD – GlaxoSmithKline Biologicals SA (GSK) and Nabi Biopharmaceuticals have announced an exclusive worldwide option and licensing agreement for a nicotine conjugate candidate vaccine (NicVAX®), an investigational vaccine for the treatment of nicotine addiction and the prevention of smoking relapse, as well as for the development of a second-generation nicotine vaccine.

Under the terms of the agreement, GSK will pay to Nabi an upfront non-refundable fee of $40 million at closing and will receive an option to exclusively in-license NicVAX® on a worldwide basis and a license to develop follow-on next-generation nicotine vaccines using Nabi's intellectual property. Together with the upfront payment, Nabi is eligible to receive over $500 million in option fees and regulatory, development, and sales milestones for NicVAX® and follow-on nicotine vaccines. Nabi will also receive double-digit royalties on global sales of NicVAX® should GSK exercise its option, as well as royalties on global sales of next-generation nicotine vaccines.

NicVAX® has recently entered the first of two Phase III clinical trials. Nabi will be responsible at its cost, for the Phase III development of this candidate vaccine. Upon successful completion of the Phase III studies, if GSK exercises its option, GSK will take responsibility for further development and commercialization of NicVAX®. In parallel with the Phase III studies, and independent of whether it exercises its option to in-license NicVAX®, GSK will be developing a next-generation nicotine vaccine based on Nabi's intellectual property together with GSK's own technology.

"If approved, this smoking cessation vaccine technology could be a novel solution to help the millions of smokers who want to stop smoking and remain abstinent; a habit that is well documented to be very hard to stop permanently," said Jean Stephenne, president of GSK Biologicals. "This technology builds our capability in the therapeutic uses of vaccines and is a great addition to our smoking cessation portfolio."

"We are very pleased with this deal and proud it is with GSK, one of the world's leading vaccine companies, to further develop and commercialise NicVAX®," said Dr. Raafat Fahim, president and chief executive officer of Nabi Biopharmaceuticals. "We look forward to addressing one of the largest unmet medical needs of our time with what we believe will be an effective tool to help people quit smoking and remain smoke-fee for the rest of their lives."

Tobacco use is the leading cause of preventable death in the world. Smoking is a global epidemic, affecting an estimated 1.2 billion smokers worldwide and is responsible for 5.4 million deaths per year worldwide. Nicotine dependence is a chronically relapsing condition, with only a minority of smokers achieving permanent abstinence in the first attempt to quit. Tobacco has been recognized by the Royal College of Physicians as being on par, from an addictive standpoint, with heroin and cocaine, and as such, many tobacco users need support to stop.

The vaccine is designed to stimulate the immune system to produce antibodies that bind to nicotine. A nicotine molecule attached to an antibody is too large to cross the blood-brain barrier. Therefore, NicVAX® blocks nicotine from reaching its receptors in the brain and prevents the highly addictive pleasure sensation experienced by smokers and users of nicotine products.

Pre-clinical and clinical data show that NicVAX®'s ability to block nicotine from reaching the brain could help people quit smoking. Because the body's immune system can be boosted to produce long-lasting antibodies, Nabi believes the candidate vaccine could also be effective in preventing smoking relapse. Relapse is a significant challenge facing smokers. Currently available smoking cessation therapies have relapse rates that can be as high as 90% in the first year after a smoker quits.

Galenix and DSM Sign Manufacturing and Marketing Accord

In-PharmaTechnologist.com: November 12, 2009 – French drug delivery specialist Galenix has named DSM's pharmaceutical products unit as its manufacturing and co-marketing partner as it continues efforts to build its global presence. The deal will see Dutch chemicals giant DSM act as the preferred commercial-scale producer of Galenix' range of delivery and bioavailability-enhancement platforms, which include the Minextab, Mucolys, and Microgix excipient technologies.

Galenix has sought to grow its offering in the lucrative U.S. pharmaceutical market since late 2004, when it set up a business office in New York, and DSM is the latest stage in that expansion plan according to CEO Jerome Besse. He explained that "The partnership fits with our strategic intention of expanding service offerings to the North American market, and also with DSM's expansion of sales and marketing focus in Europe."

Pieter de Geus, DSM senior vice president of R&D was equally positive about the accord, suggesting "The innovative drug delivery technologies enhance our offering in the field of pharmaceutical development services. The firms will also work on

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business development and co-marketing for both Galenix' development and clinical services offering and DSM's contract pharmaceutical manufacturing, process development and scale-up expertise." DSM Pharmaceuticals President Hans Engels said, "The alliance brings out the best of both parties. Combining innovative formulations with flawless transition into commercial products creates an attractive value proposition for any drug company."

PharmaForm Rolls Out Contract Spray-drying Service

In-PharmaTechnologist.com: November 5, 2009 – U.S. contract manufacturing organization (CMO) PharmaForm has added spray-drying to its contract offering to capture a share of the ever-present market for drug bioavailability enhancement.

The CMO has installed an Anhydro MicraSpray 35 unit at its plant in Austin, TX, in a move that CEO Gregory McKee said is part of a strategic focus on poorly soluble compounds. He explained that "Spray drying further enables us to better serve our clients by offering another proven…technology to enhance bioavailability and accelerate their drug development programs."

The addition of spray-drying capacity is the latest in a wide-ranging restructuring program at PharmaForm since the merger of parent company Akela Pharma with Nventa Biopharmaceuticals in May. In September, PharmaForm reduced its workforce by 65 employees and set out plans to close some of its international units and consolidate its U.S. operations in a bid to enhance its client support infrastructure.

Abraxis Dedicates Nanobiologics Site

In-PharmaTechnologist.com: November 5, 2009 – Abraxis Health has dedicated its manufacturing facility in Phoenix, AZ, which is the result of a $70 million (€47 million) investment to give the company the nanotech and biologics capacity needed for Abraxane production.

From 2004 to 2007 Abraxis set about boosting its manufacturing capacity in anticipation of increased demand for the cancer treatment Abraxane (paclitaxel protein-bound particles for injectable suspension) and its pipeline of pharmaceuticals. One aspect of this was the purchase of the 200,000-ft^2 sterile-injectables Phoenix site, which also houses chemistry and microbiology laboratories, from Watson Pharmaceuticals in 2007.

Abraxis has revamped the site to make it "the world's largest and most sophisticated protein nanobiologics manufacturing plant" and equip the company for growth. Following the improvements, the site will be capable of producing 10-million units a year, and this could be expanded to 20 million in the future. There is also the possibility that Abraxis will invest in new technology and equipment in the future.

The facility needs to be checked by the U.S. Food and Drug administration and European regulators before commercial production can begin. This is due to happen in late 2010. Improvements to the facility will create up to 200 high-tech jobs. Abraxis has hired more than 100 former Watson employees and recruited additional staff since it bought the site in 2007.

The company plans to further expand its workforce as production increases. This could occur in response to increased demand for Abraxane, but the technology at the Phoenix facility is also being used in multiple agreements for the development of novel, insoluble compounds.

Genzyme Targets BBB

In-PharmaTechnologist.com: November 4, 2009 – Genzyme is evaluating to-BBB's G-Technology as part of a research collaboration aimed at developing treatments capable of crossing the blood-brain barrier (BBB). The BBB currently poses a substantial obstacle to drug companies developing treatments for central nervous system (CNS) disorders, hindering progress in the creation of medicines for diseases, including Alzheimer's and cancer.

Dutch brain drug delivery company to-BBB believes its G-Technology has the potential to overcome this obstacle and facilitate the delivery of a wide range of molecules, in particular biologics, to the brain. G-Technology consists of liposomes coated with glutathione-conjugated polyethylene glycol (PEG). The therapeutic is encapsulated in the liposome, which is coated with PEG to prolong circulation time, and this protects it from degradation and immune response.

The other element of the delivery technology is glutathione, a naturally occurring anti-oxidant found in high levels in the brain. Glutathione receptors are found at the BBB, and these facilitate the movement of the therapeutic into the brain. to-BBB has performed proof-of-concept studies using peptides and small molecules and is developing an internal pipeline of products using G-Technology, including 2B3-101, a brain cancer treatment that is due to enter clinical trials in the second half of 2010. In addition to this internal development, to-BBB has relationships with Shire, MedImmune, and Genzyme. The research collaboration with Genzyme is focused on neurodegenerative diseases.

Under the terms of the agreement, Genzyme will evaluate G-Technology in its disease models to "explore an essential component of its work to deliver therapies to the brain," according to Geoff McDonough, senior vice president at the biotech. Willem van Weperen, CEO of to-BBB, added, "Combining the expertise of Genzyme in neurodegenerative diseases with to-BBB's brain delivery knowledge, should lead to further progress in treating patients with brain diseases with biological drugs."

Novartis Invests in China

In-PharmaTechnologist.com: November 3, 2009 – Novartis is investing $250 million (€170 million) to construct a facility in China focused on the research, development, and manufacture of APIs and has earmarked a further $1 billion to expand its R&D activities in the country. The investment is a significant expansion

of Novartis' activities in China, which will become the big pharma's third largest R&D region, as it attempts to capitalize on the cost-effectiveness, expertise, and rapid market growth the country offers.

A $250-million global technical center will be constructed in Changshu, in east China, which will focus on the R&D and manufacture of active pharmaceutical ingredients (API). By co-locating API R&D and manufacture, Novartis believes it can realize synergies that will significantly improve pharmaceutical processes and operational efficiencies. Novartis predicts the center will become a "critical part" of its global production and supply chain network. The company already operates a facility in Changshu, which focuses on the process and analytical research and development of drugs and their manufacturing technologies, and the new center will double the number of high-quality jobs Novartis provides at the site.

The main thrust of Novartis' expansion in China is a $1-billion investment in its R&D activities over the next five years. This money will be used to significantly expand The Novartis Institute of BioMedical Research (CNIBR) in Shanghai by relocating it from its existing site. Currently, CNIBR is in Zhangjiang High-tech Park and specializes in basic R&D of drugs focused on diseases that are highly prevalent in China, but the scale of the expansion necessitates relocation. CNIBR will move to another campus in Shanghai and expand its capabilities to cover areas that include analytics and biomarkers, *in vivo* pharmacology, protein production, genomics, and imaging.

Once complete, Novartis believes the expanded CNIBR will become its third largest R&D center, after Basel, Switzerland, and Cambridge, MA, and employ 1,000 R&D associates compared with 160 currently. Novartis also expects CNIBR to extend and increase its collaborations with institutions in China to tap and cultivate the country's talent pool. The facility will develop drugs for the Chinese market, which is expected to grow rapidly as a result of government efforts, as well as those of other countries. ■

Controlled Release Society
3340 Pilot Knob Road
St. Paul, MN 55121
United States of America

Calendar of Events

2010

UKICRS Symposium 2010: Controlled Release in Drug Delivery: Right Time, Right Place
April 14
University of Hertfordshire, Fielder Conference Centre
Hatfield Business Park, U.K.
www.ukicrs.org/

First World Conference on Nanomedicine and Drug Delivery
April 16-18
Kottayam, Kerala, India
www.nanomedicine.macromol.in/

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

7th Annual World Congress for Brain, Spinal Cord Mapping and Image Guided Therapy
May 24-27
Uniformed Services University of Health Sciences
Bethesda, MD, U.S.A.
www.ibmisps.org/

Chemistry, Manufacturing & Control (CMC): Quality, Regulatory and Scientific Requirements and Strategies
June 21-22
Shanghai, China
www.cpa.org.cn

37th Annual Meeting & Expostion of the Controlled Release Society
July 10-14
Oregon Convention Center
Portland, Oregon, U.S.A.
www.controlledreleasesociety.org/main/meetings

FIP Pharmaceutical Sciences 2010 World Congress (in association with the AAPS Annual Meeting and Exposition)
November 14-18
New Orleans, Louisiana, U.S.A.
www.pswc2010.org/

2011

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