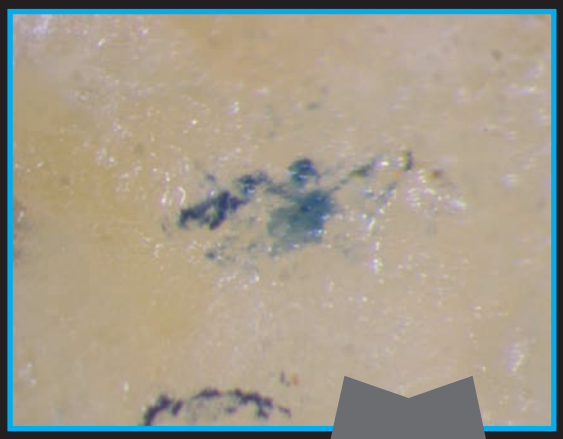
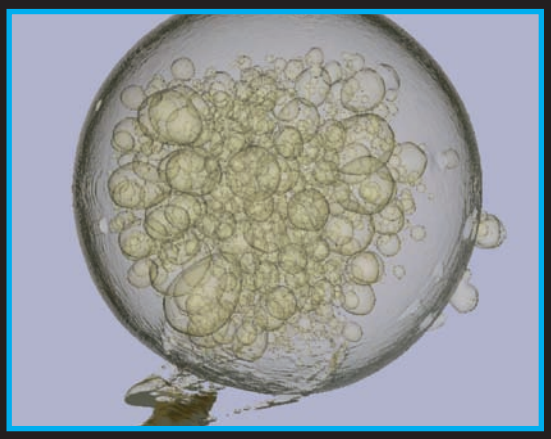
CONTROLLED RELEASE SOCIETY

Volume 24•Number 2•2007

NEWSLETTER





Check out the latest online issue of **Drug Delivery Technology** at

www.drugdeliverytech.com

Introducing

Drug Delivery Technology...online!

- No special software required
- Table of contents navigation
- Click through to advertisers' sites and content
- Print, send, and share articles with colleagues
- Interactive correspondence with editors and advertisers
- Content searchable by keywords
- Faster online distribution

CONTROLLED RELEASE SOCIETY
NEWSLETTER

Volume 24 • Number 2 • 2007

inthisissue

On the cover –

A Secret Scientist investigation.

Controlled Release Society
3340 Pilot Knob Road
St. Paul, MN 55121
+1 (651)454-7250 telephone
+1 (651)454-0766 facsimile

Visit www.controlledreleasesociety.org or e-mail crs@scisoc.org on questions about membership, meetings, publications, and services.

Contact dwoodard@scisoc.org for information about exhibiting, advertising or other visibility opportunities.

FROM THE *Editors*

By Steven A. Giannos, M.S.
Chrono Therapeutics, Inc., U.S.A.

Steven A. Giannos

I don't know about you, but after the ice and snow of this past winter, I'm ready to hear about some hot topics, hot science, and new developments in the world of controlled release. The sunny shores of Long Beach, California, beckon, and I hope everyone has made their travel plans for this year's annual meeting. The 34th CRS Annual Meeting & Exposition, July 7–11, 2007, will be the locale to hear about scientific research, meet colleagues, discuss the topic of the day, and enjoy the California sun. Many thanks to Scientific Secretary Martyn C. Davies and the 2007 Program Chairs who have organized an exciting program for our members.

Starting on Saturday, July 7, you won't want to miss the three CRS Educational Workshops, which will lead this year's annual meeting. This year's workshops include 1) the Micro- and Nanoencapsulation: Formulation, Applications, and Processes 2-day workshop (July 7–8) chaired by Paul Richardson and J. Chris Soper; 2) the Molecular Imaging and Drug Delivery workshop chaired by Alexei Bogdanov and Zheng- Rong Lu; and 3) the Sustained Release Parenteral Products: *In Vitro* and *In Vivo* Considerations workshop chaired by Marilyn Martinez and Mike Rathbone.

For our Young Scientists, exciting new hands-on workshops are being offered by the Consumer & Diversified Products Committee that will cover controlled release in personal care, food applications, and fragrances; fluid bed technology; IP search of CR technologies; flavor delivery systems; and encapsulation systems for industrial applications. There will even be a display booth to view C&DP products and experts available to ask all about them.

Sunday offers Highlights of Student Posters, Pearls of Wisdom, Releasing Technology Workshops, and, my favorite, the ever-popular and fast-paced Soapbox Sessions.

Plenary sessions include Steven Buchsbaum (Bill and Melinda Gates Foundation), Joseph DeSimone (University of North Carolina) will present "Organic Delivery Vehicles for Probing and Treating Biological Systems: Adapting Fabrication Processes from the Electronics Industry for Use in Nano-medicine." You'll want to hear about the "WHO Perspective on Vaccine Research and Development" presented by Marie-Paule Kieny (World Health Organization). Prof. Teruo Okano's (Tokyo Women's Medical College) topic of discussion is "Cell Sheet Tissue Engineering and Their Clinical Applications." Patrick Soon-Shiong (Abraxis Bio Science) will give a talk on "Receptor-Mediated Transcytosis: A Biologically Interactive Delivery Pathway—The First Clinical Application in Cancer Therapy." To complete this outstanding scientific display, be sure to hear David Tirrell (California Institute of Technology) present "Artificial Proteins and Artificial Amino Acids."

A first for CRS will be the Juvenile Diabetes Research Foundation co-sponsored mini-symposium Recent Delivery in Diabetes. Delivery for Bioimaging; Gastroretention-Animal vs. Human; Liposomes: Alive & Kicking; and Stimuli Responsive Nanosystems

round out the mini-symposia offerings in Long Beach. With such diverse topics, you'll definitely find those that fit you and your areas of interest.

Inside this issue of the *CRS Newsletter*, check out what's developing in the area of ceramic microsphere encapsulation by CeramiSphere, gene transfection from the Tokyo Medical and Dental University, the Secret Scientist, news from CRS chapters, as well as transdermal patent reviews, "In the News," and other regular features.

As always, we encourage all members to continue to give thought to submitting articles to the *Newsletter*. Those in small companies and start-ups, as well as academia, are encouraged to contact the editors and submit material that describes their novel and significant technologies. We also appreciate hearing about "hot topics" in science, faculty and student awards, and other worthy news.

On behalf of the *CRS Newsletter* editorial team, we hope to see you all in Long Beach this summer!!! ■

Bookmark It!

www.controlledrelease.org/meeting

for updated information on the 34th Annual Meeting & Exposition of the Controlled Release Society.

LONG BEACH

CALIFORNIA

Photos courtesy of the Long Beach Area Convention & Visitors Bureau.

34th Annual Meeting & Exposition of the Controlled Release Society

July 7–11, 2007
Long Beach Convention Center
Long Beach, California U.S.A.

✦✦✦

Plenary Speakers & Topics

- Improved Childhood Vaccines—A Grand Challenge in Global Health
  Steven Buchsbaum
  Bill and Melinda Gates Foundation, U.S.A.
- Organic Delivery Vehicles for Probing and Treating Biological Systems: Adapting Fabrication Processes from the Electronics Industry for Use in Nano-medicine
  Joseph M. DeSimone
  University of North Carolina, U.S.A.
- Cell Sheet Tissue Engineering and Their Clinical Applications
  Generously Sponsored by NOF
  Teruo Okano
  Tokyo Women's Medical College, Japan
- Receptor-mediated Transcytosis: A Biologically Interactive Delivery Pathway—The First Clinical Application in Cancer Therapy
  Patrick Soon-Shiong
  Abraxis BioScience, Inc., U.S.A.
- Artificial Proteins and Artificial Amino Acids
  David A. Tirrell
  California Institute of Technology, U.S.A.

✦✦✦

Registration Is Now Open

Interested in Exhibiting?
Visit the website for more information.

www.controlledreleasesociety.org

Randall Mrsny
CRS President

From the President

The Controlled Release Society—A Scientific Entity Serving a Diverse Group of Scientists

By Randall Mrsny
Welsh School of Pharmacy, University of Wales, Wales, U.K.; and Trinity BioSystems, Inc., Menlo Park, CA, U.S.A.

Our society has evolved over the last 35 years. From an initial group of agrochemical scientists in 1973 who had an interest in modulating the release rate of materials from polymers, the Controlled Release Society (CRS) has grown to approximately 3,000 members from more than 50 countries with a tremendously diverse range of interests and backgrounds. Currently, our members are trained in areas of biology, chemistry, and physics, as well as human and animal medical practice. Their interests include improving cosmetics, vaccines, therapeutics, surgical procedures, and cancer treatments, to name just a few. What brings this diverse group together year after year, making the CRS a premier scientific forum? From my perspective, the answer is both complex and simple. By understanding issues from their most complex aspects, one can find simple truths that lead to great leaps in our scientific understanding. This is what I think the CRS is about—a diverse group of individuals working together to derive simplicity from complexity.

As much as the CRS has evolved to allow for the integration of the many different types of scientists who come together to derive simplicity from complexity, the methods and elements that allow this to occur continue to change. The CRS Board of Directors recognizes the importance of our society continuing its evolutionary process to maintain its position as a premier scientific forum. There are at least two aspects of this process that I feel will be important to our evolution as a society: maintaining an environment where our current members can continue to have a forum that is relevant to wherever their science takes them and presenting an environment that entices those looking in from the outside to join. Success in both of these areas is dictated to a great extent by image. Our members will leave and join (or start) new societies if their image of the CRS suggests that their science no longer fits. Potential new members will not join if they perceive that the CRS cannot provide the scientific environment they desire.

The confluence of these two issues, evolution and image, brings me to the topic of this letter—is it time for the CRS to undergo a re-branding that better defines where the society currently stands and where it is likely to go in the future? The Board of Directors believes that it is time to change the image of the society to better represent the evolution the CRS has undergone and will likely undergo in the near future. The biggest aspect of this image change is to better represent the immense breadth of the society and its dynamic nature as it incorporates new scientific fields. Although my superficial survey (I am well aware that an $N = 10$ of CRS members does not define our society) supports the board's interest in re-branding, I would like to hear from anyone who would like to voice positive or negative points regarding such a strategy. After all, these may have been friends just trying to be nice.

At present, the society is planning to expand its presence in several areas. We have initiated an effort to publish our own series of books on the many technologies derived by our CRS members. We are planning to increase our international presence through participation and/or initiation of various conferences and symposia. We will soon begin the process of re-negotiating the contract with the publisher of our society's journal. Our aim will be to maintain the *Journal of Controlled Release* as the premier site for cutting-edge, original work in the areas of interest to our membership. We also will begin exploring potential associations with other societies to increase our exposure and presence in the scientific community in general. Overall these efforts are focused on maintaining and extending our position as the leading scientific society where the many disciplines and interests that make up the CRS can come together.

The board believes that a streamlined, modern logo will better present and represent the Controlled Release Society in the areas discussed above. We already define ourselves by the acronym of CRS. The board felt that these three letters could provide an accurate yet sufficiently generalized description of the society and that these three letters were already familiar to the membership. In some ways we are copying what IBM did years ago; once the company realized it had outgrown the initial specialties from which the company was started as International Business Machines, it wanted to change its image and re-branded itself as IBM. Such a re-branding honored its heritage and simultaneously allowed it to look to the future. We wish to do essentially the same thing by re-branding the Controlled Release Society as CRS.

No final steps have been taken on the path to re-brand the Controlled Release Society as CRS. We are moving thoughtfully and cautiously to ensure that this is the right thing for the society and, thus, for our membership. Right now we believe this effort, which will appear as a relatively minor change on book covers, letterhead, and meeting programs will ultimately be very beneficial to the society in the future. I look forward to hearing any comments or thoughts you have regarding re-branding of the CRS. Remember, this is your society. Your voice (and your vote—see the last president' message) is heard, and it can make a difference. ■

34th CRS Annual Meeting & Exposition

See You in Long Beach!

The 34th Annual Meeting & Exposition of the CRS is just around the corner! When packing for this event in Long Beach, California, be sure to include plenty of business cards to share with your new friends, future colleagues, and those you are always happy to see at the CRS. Remember the sunscreen, too, for strolling in this great American walking city.

The science slated for the July 7–11, 2007, Annual Meeting & Exposition is like no other you'll attend this year. Scientific Secretary Martyn C. Davies and 2007 Program Chairs You Han Bae, Alexander Kabanov, Derek O'Hagan, Doug Dale, Chuck Frey, Craig Bunt, and Sevda Senel have planned an innovative and exciting program for you.

The 2007 Program Committee has a full complement of Plenary Speakers heading to Long Beach to bring you the most recent results and discoveries in controlled release and delivery. Steven Buchsbaum (Bill and Melinda Gates Foundation) is one of six Plenary Speakers for CRS in 2007. Joseph DeSimone (University of North Carolina) will present "Organic Delivery Vehicles for Probing and Treating Biological Systems: Adapting Fabrication Processes from the Electronics Industry for Use in Nano-medicine." You'll want to hear about the "WHO Perspective on Vaccine Research and Development" presented by Marie-Paule Kieny (World Health Organization). Prof. Teruo Okano's (Tokyo Women's Medical College) topic of discussion is "Cell Sheet Tissue Engineering and Their Clinical Applications." Patrick Soon-Shiong (Abraxis Bio Science) will give a talk on "Receptor-Mediated Transcytosis: A Biologically Interactive Delivery Pathway—The First Clinical Application in Cancer Therapy." To complete this outstanding scientific program, be sure to hear David Tirrell (California Institute of Technology) present "Artificial Proteins and Artificial Amino Acids."

Opportunities abound at the CRS Annual Meeting & Exposition. From the outstanding science to be presented to the Exhibitors ready to meet your research needs, you'll find everything you need. The CRS Exhibit Hall will be home to more than 100 of the leading companies in the controlled release and delivery industry, helping you find the latest products, technologies, publications, and services. The kick-off event in the Exhibit Hall will be the Welcome Reception on Sunday, July 8. The CRS schedule makes networking in the Exhibit Hall easy, with numerous breaks taking place Monday through Wednesday, July 9–11. Take advantage of time in the Exhibit Hall, and use the Exhibit Hall floor plan to map your stops.

CRS Long Beach features more than 45 invited speakers who will highlight their research in the hot topics of controlled release and delivery, more than 100 submitted oral presentations, and 2 poster sessions that will draw your full attention. With too much to see and do, the CRS 34th Annual Meeting & Exposition *Transactions* CD-Rom will come in handy after the meeting has ended.

CRS Long Beach will offer seven Releasing Technology Workshops on Sunday, July 8. The RTW hosts will be Altea Therapeutics, Capsugel, ChemImage Corporation, CMA/Microdialysis, Colorcon, Fuji Health, and Genzyme. There's something for everyone at these workshops! CRS is also mixing the ever-popular Soapbox Sessions up a bit at the Annual Meeting & Exposition. Sunday, July 8, will showcase 26 companies, and 5 companies will open the Industrial Session on Tuesday, July 10. Be ready to hear the latest in new ideas and meet with potential collaborators.

CRS is honored to be hosting the Recent Delivery in Diabetes mini-symposium with the Juvenile Diabetes Research Foundation. The presenters featured will be Bruce Buckingham, Julia Greenstein, Aaron Kowalski, David Scharp, W. Kenneth Ward, and William McGarity. Delivery for Bioimaging speakers will be Samuel Achilefu, Alexi Bogdanov, Zheng-Rong Lu, and Karsten Maeder. The Gastroretention—Animal vs. Human presentations will be given by Keith Ellis, Marilyn Martinez, Kazuko Sagawa, and Clive Wilson. Liposomes: Alive & Kicking invited speakers are Leaf Huang, Raymond Schiffelers, Stavroula Sofou, and David H. Thompson. Rounding out the mini-symposia offerings in Long Beach will be Stimuli Responsive Nanosystems with You Han Bae, Tatiana Bronich, Nobuhiro Nishiyama, and Patrick Stayton. With such diverse topics, you'll definitely find your areas of interest.

Saturday, July 7, will include one 2-day and two 1-day CRS educational workshops and the opening of the 2-day Young Scientist Workshop. Remember, the Young Scientist Workshop is complimentary to those 40 years of age and younger or those new to controlled release and delivery within the past five years.

Young Scientist events are complimentary with your Annual Meeting & Exposition registration. Even though these workshops and the Get Up; Get Educated sessions are complimentary, you must register to secure a seat. The Young Scientist events fill up quickly!

Saturday, July 7, will bring the first installment of the Young Scientist Workshop. Chairs Farid Dorkoosh and Roderick Walker have selected experts to focus on Basic Pharmaceutical Science and Manufacturing Principles. Speakers and their topics are Juergen Siepmann – Diffusion; Thomas Rades – Solubility; Alexander Florence – Flow, Rheology and Viscosity; Glen Kwon – Polymeric Surfactant Chemistry; Sven Frokjaer – Colloid Chemistry; Wim Hennink – Hydrogels: Preparation, Characterization and Pharmaceutical Applications; Rod Walker – Controlled Release Tablet and Pellet Technologies—An Overview; Brian A. C. Carlin – Formulation and Processing of Multiparticulate Sustained Release Systems and Formulation and Processing of Matrix Sustained Release Systems; Nasser Nyamweya – Formulation and Processing of Methacrylate Multiparticulate Sustained Release Systems; Bridgitte Skalsky – Functional Film Coating—Processes, Parameters, Formulations; and Vishal Gupta – Considerations of Solubility and Other Physico-chemical Characteristics in the Development of Oral CR Dosage Forms.

On Sunday, July 8, the Young Scientist Workshop will continue with a new hands-on workshop organized by the Consumer & Diversified Products Committee that will feature presentations by Doug Dale, Nava Dayan, Charles Frey, Anil Gaonkar, Claudio Ortiz, Ron Versic, and Teresa Virgallito. Be sure to visit the workshop's booth located outside the session room to ask the C&DP experts your questions and take a look at the C&DP products and equipment on display.

For you early risers, the Get Up; Get Educated sessions will be held on Monday, July 9, and Tuesday, July 10. Monday will feature Brian Crist discussing "The Basics of *In Vitro* Dissolution Testing." Tuesday will feature Raimar Loebenberg presenting "*In-Vitro/In-Vivo* Correlation."

The Micro- and Nanoencapsulation: Formulation, Applications, and Processes 2-day educational workshop (July 7–8) will offer attendees the opportunity to learn the basic concepts of various controlled release technologies, information on release mechanisms, and behaviors of key technologies in commercial use. The educational workshop, Molecular Imaging and Drug Delivery, will be held on Saturday, July 7, and will address hot topics in molecular imaging and drug delivery, cover how molecular imaging could assist in drug development and translational research, non-invasive issues, such as evaluating therapeutic response with dynamic MRI, and visualization of *in vivo* drug delivery with polymers. The Sustained Release Parenteral Products: *In Vitro* and *In Vivo* Considerations educational workshop will also be held on Saturday, July 7. The workshop will discuss the considerations and challenges

Courtesy of the Long Beach Area CVB.

associated with the development of discriminative and biologically relevant *in vitro* methods for assessing drug release for parenteral products, identify critical biopharmaceutical issues, such as the important physiological variables influencing drug release and the impact of altering injection volume and concentration, address the possibility of establishing *in vitro* and *in vivo* correlations, and provide attendees an opportunity for an exchange from two perspectives—human and veterinary.

Talk about HOT topics. Be sure to take in a Pearls of Wisdom debate. Justin Hanes will be hosting the "Viral Vectors" debate between John Chiorini and Leaf Huang. Sevda Senel will moderate the "*In Vitro* Drug Release Tests Are Invaluable Tools in Veterinary Product Development and Quality Control," featuring Michael Rathbone and Avinash Thombre. During the C&DP tennis match, Chuck Frey will be the perfect judge. Witness the ball getting bounced around while discussing "Nanotechnology: Economic Benefit or Potential Hazard." Be ready to be engaged and entertained. Caution: can cause outbursts of laughter!

CRS has once again secured great hotel room rates at facilities you'll enjoy. Within close proximity to the Long Beach Convention Center, you'll find the CRS home away from home that fits your needs. Make your hotel reservations directly with the hotel of your choice by telephone or online. To ensure a room in the hotel you prefer, please make your reservations early. Select from the Hyatt Regency Long Beach, Renaissance Long Beach, and Westin Long Beach. Visit www.controlledreleasesociety.org for more details on these CRS host hotels.

Come to Long Beach prepared to meet the future. See you there! ■

Secret Scientist

In this issue, the Secret Scientist ruthlessly investigates a critical ELISA problem

Dear Secret Scientist,

My enzyme-linked immunoassay (ELISA) does not give me consistent results. We use this method to determine whether serum samples contain antibodies against our experimental adjuvants, so samples are serially diluted across adsorbent plates, allowing antibody in serum samples to bind to adsorbed antigen. While this technique has worked well for me in the past, I am now getting an unacceptably high background reading. I am following a standard procedure that has been used in our laboratory for some time. Why is it not working for me now? Please help.

The Secret Scientist says:

ELISA can be used in laboratories to determine whether a particular antibody is present in serum, and the many different ELISA protocols available allow the application of this technique for varied and diverse diagnostic and analytical purposes.

While posing as a cleaner in a top U.K. research lab, the Secret Scientist quizzed researchers, technicians, and anyone who had an opinion about the worrying problem faced by our reader.

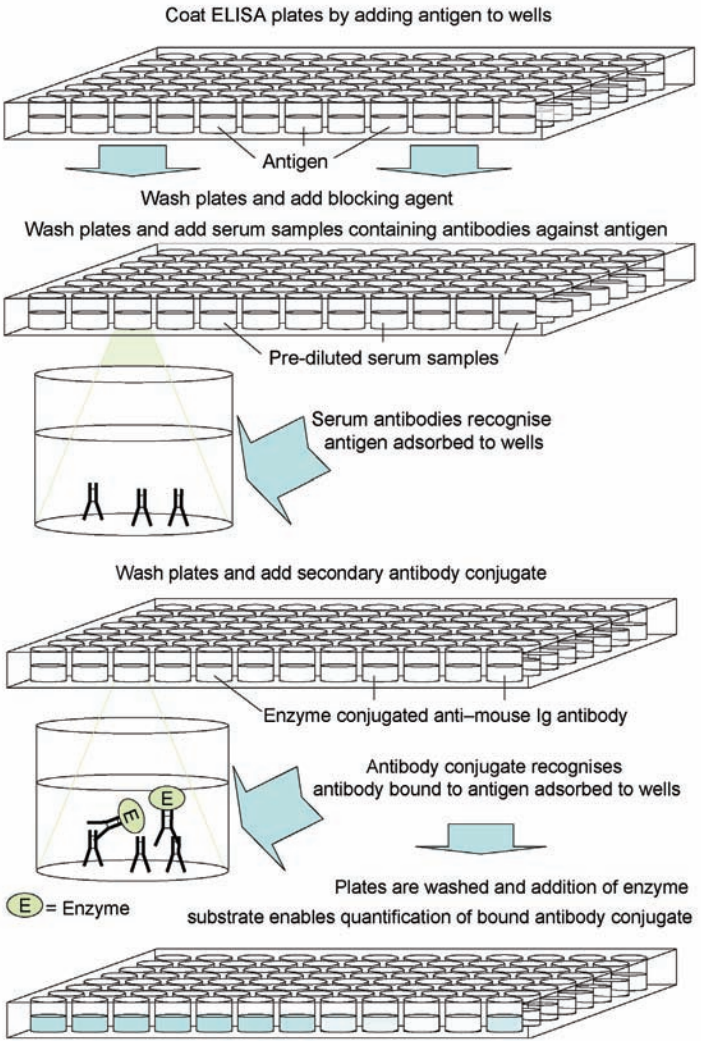
Here are some answers the Secret Scientist found:

A number of variables are routinely incorporated into the ELISA protocol, and if not optimized correctly, these can adversely affect the outcome and sensitivity of the assay. Reagent selection, including coating buffer and development reagent, aliquot and washing volume, incubation time and temperature, type and concentration of blocking buffer, among other things, can all have effects.

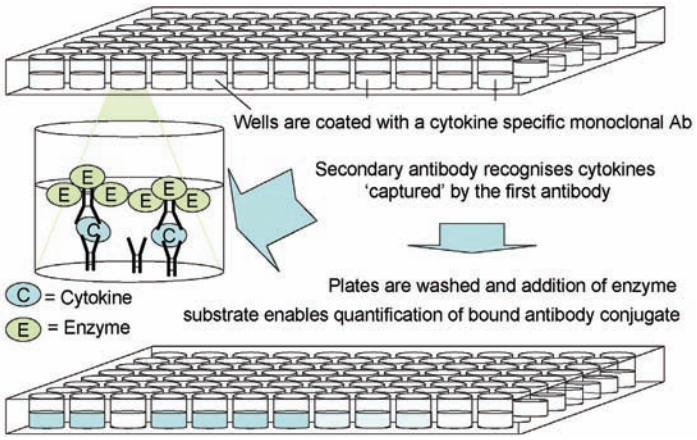
Some interesting tips for reducing background readings and possibly increasing sensitivity of standard serum antibody ELISA protocols are

- Ensure that evaporation of samples from the wells does not occur during incubation steps. This can lead to precipitation of proteins or reagents at the top of the sample and give false readings. Evaporation can be avoided by incubation in a humid environment or sealing the plates with adhesive strips.
- It is important to optimize the concentration of your secondary antibody. The specific activity of secondary antibodies varies between manufacturers. Re-optimization should be performed when one or more of the experimental variables, such as the antigen, secondary antibody, or substrate, is changed. This can be achieved easily through the use of different concentrations on the same plate, using the manufacturers' recommended dilution as a starting point.
- Try a different blocking reagent. One researcher reported a massive reduction in background after switching the blocking reagent from bovine serum albumin (BSA) to non-fat dried milk (Marvel). In this case, anything from 1 to 4% Marvel in PBS was the best of the options tried. There was also a cost saving, as Marvel is significantly cheaper.
- Optimize your washing protocol. Today most people use an automatic plate washer. These are variable in their specifications, and it is possible to alter aspiration height from the wells (sometimes manually), washing volume, and number of washes. Successful parameters should be checked (ideally they should be optimized) and noted (they could have been changed and may not be specified in your protocol). You may also find that it is better if plates are inverted and residual liquid blotted out onto absorbent cloth before adding the next aliquot.
- Look after your plate washer. Wash buffer will cause the washer to become blocked if allowed to dry in the dispensing head. The head should always be emptied and, if possible, rinsed with distilled water. Even slight blocking that you might not notice easily, especially with a 96-well head, may impair washing and give false readings.
- Use fresh buffers. PBS and PBST can be cheaply made up from their basic constituents (as we all conveniently forget when we order expensive PBS tablets). An old or contaminated buffer can lead to higher background levels by more than one mechanism. Taking a risk with buffers will prove to be a false economy in the long run—at best compromising your reproducibility and sensitivity and at worst costing valuable samples and ruining experiments.
- Respect your protocol. Any changes in protocol may require different levels of care and attention. For example, when using *p*-nitrophenylphosphate (PNP) substrate, just touching the PNP substrate solution or reservoirs can result in phosphatases from the skin initiating colour development of the PNP substrate. PNP, as well as trimethyl benzidine (TMB), are both light sensitive. Different buffers may be required for adsorption of your antigen to ELISA plates. For example, PBS at physiological pH may be suitable for diphtheria and tetanus toxoids, but 0.05*M* sodium carbonate buffer at a pH above pH 9 may be more suitable for hepatitis B surface antigen.

ELISA Protocol:
Standard ELISA for quantification of antigen-specific antibodies in serum



ELISA Protocol:
Cytokine quantification by capture ELISA



Don't be afraid to throw out your old protocol and try bold new conjugates, development reagents, and varied protocols. Remember to do all your optimization in such a fashion that you can apply statistical analysis (i.e., at least $n = 3$). It may feel unproductive or even tedious, but such optimization data may also provide a valuable contribution to a thesis and will undoubtedly increase your understanding of ELISA, helping to set up a robust assay for the future for yourself as well as others.

Hopefully these tips uncovered by the Secret Scientist will prove to be useful. If you are having problems that you are having a difficult time solving, contact the Secret Scientist. Send your tricky lab problems to Yvonne (y.perrie@aston.ac.uk) who will pass your problem on to our Secret Scientist. ■

Call for 2008 CRS Workshop Applications

It's time to collect your thoughts and submit your ideas. What educational workshop would you like to chair at the CRS annual meeting in New York? Be sure to read all about the chair guidelines and responsibilities and review the application on the CRS website before you begin the process. Workshops must be of high educational value for attendees and financially sound for CRS. In order to be considered, completed applications must be received by June 8, 2007. Applicants will be notified of application status on or before September 10, 2007.

Scientifically Speaking

Gene Transfection on Tissue Engineered Bone Decellurized by Ultra-High Hydrostatic Pressurization

By Tsuyoshi Kimura, Seiichi Funamoto and Akio Kishida
Institute of Biomaterials and Bioengineering
Tokyo Medical and Dental University, Tokyo, Japan

Introduction

The development of scaffold, which contributes to adhesion and expansion of cells that can regenerate tissue lost to disease, is one of the key factors in tissue regeneration. Many researchers have investigated polymeric scaffolds, such as poly(lactic acid) (1), poly(glycolic acid) (2), hyaluronic acid (3), and collagen (4). It has been reported that the shape and microscopic structure of these scaffolds, such as porous, fibrous, and gel, plays an important role in tissue formation, as does the physical and physicochemical nature of the scaffold (5). However, it is difficult to obtain the same shape and structure as the biological tissue. Therefore, there is an alternate approach for preparing scaffold that is similar to the natural scaffold that uses decellularized tissues from which the cells and antigen molecules have been removed to diminish the host immune reaction. The decellularized scaffold is thought to have the same structure and composition as the natural tissue, and the regeneration within the scaffold is expected to be regulated by donor cells. Detergents, such as Triton® X-100 (6), sodium dodecyl sulfate (7), and sodium cholate (8), generally are used to remove the donor cells and their components. The remainder of the detergents, the residual cellular component in the scaffold, and the denaturing of tissue are reported to be important problems. We have also reported on the development of tissue engineered bone by novel physical decellularization process using ultra-high pressure (UHP) technology without surfactant (9). This decellularization method involves two processes. As a first step, cells, bacteria, and viruses in the tissue are disrupted by ultra-high pressurization. Subsequently, the residues of disrupted cells are removed by washing (Figure 1).

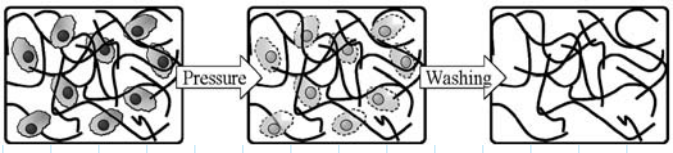


Figure 1. Preparation procedure for decellularizing tissue using ultra-high pressure treatment.

Recently, the focus has been the combination of tissue engineering scaffold and gene therapy, which provide the physical support for cell adhesion and cellular functioning by delivering the gene (10). For *in vitro* gene delivery, non-viral vectors, such as cationic polymers, cationic lipids (11), and calcium phosphate (12), have been used for stabilization of DNA, resulting in effective gene transfection. On the other hand, when they are applied in a living body, their cytotoxicity and low transfection efficiency likely will become considerable problems. For bone regeneration, it is thought that calcium phosphate, which is one component of bone, is suitable as a gene carrier because it is able to form a co-precipitate with DNA for gene transfection and to become bone by itself.

In this study, we demonstrated the preparation of decellularized bone by pressurization and gene transfection to reseeded cells on the decellularized bone with co-precipitates of calcium phosphate with plasmid DNA *in vitro*.

Results

Porcine bones (femur and costa) were cut and shaped and then pressurized at 25°C and 10,000 atm (980 MPa) for 10 min (UHP treatment). After UHP treatment, they were washed by culture medium containing DNase I at 37°C for 2 weeks. The decellularization of bone was evaluated by hematxylin and eosin (H-E) staining. Figure 2 shows that the removal of cells in bone and bone marrow of femur was completely achieved by UHP treatment. The porous structure of bone and the fibrous structure of collagen, along with lipid droplets in bone marrow, were well maintained. The decellularized costa also was prepared by UHP treatment. MC3T3 cells (1×10^5 cells) were reseeded on the decellularized bone *in vitro*. After cultivation for 3 days, the

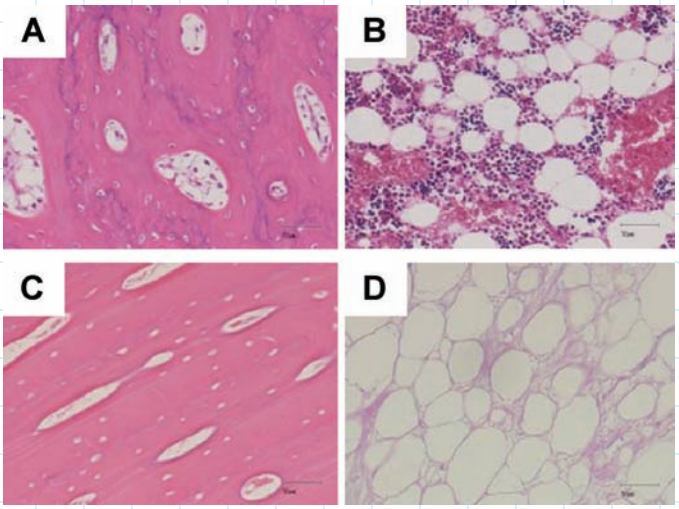


Figure 2. Hematoxylin eosin staining of (A) native cortical bone, (B) native bone marrow, (C) decellularized cortical bone, and (D) decellularized bone marrow by pressurization at 10,000 atm (980 MPa) for 10 min.

adhesion and extension of cells on the surface of the decellularized bone was observed at the outside and the inside of the bone under scanning electronic microscopy (SEM). The decellularized femur was implanted subcutaneously in rats to investigate their biocompatibility. After 2- and 4-weeks implantation, they were explanted and subjected to histological study (H-E staining). Light microscopic observation confirmed that a strong inflammatory response was observed on native bone after 2 weeks. Fibrous encapsulation and gradual collapse of bone marrow occurred after 4 weeks. On the other hand, very thin fibrous encapsulation was observed around the decellularized femur. The re-construction of tissue by infiltration of cells in decellularized bone marrow also was observed after 4 weeks, suggesting the capability of the decellularized bone as a bio-scaffold.

Plasmid DNA encoding beta-galactositase gene under cytomegarovirus promoter (pCMV-beta: clonetech) was used. A solution of pCMV-beta was mixed with $CaCl_2$ solution (2*M*) and added to 2× HBS solution to form the co-precipitate of pCMV-beta and calcium phosphate. The decellularized bone was immersed in the mixture at 37°C for 30 min. MC3T3 cells (5×10^4 cells) were reseeded on the decellularized bone and cultivated for 3 days. The gene transfection was evaluated by X-gal staining. Without co-precipitation, there was no change in cells reseeded on the decellularized bone with only DNA, whereas blue-stained cells were observed on the decellularized bone with calcium/DNA co-precipitate (Figure 3), indicating effective gene expression by the combination of the calcium phosphate co-precipitate method and tissue engineered bone. This result indicated that decellularized tissue was significantly useful in the novel combination of the tissue engineered scaffold and gene delivery.

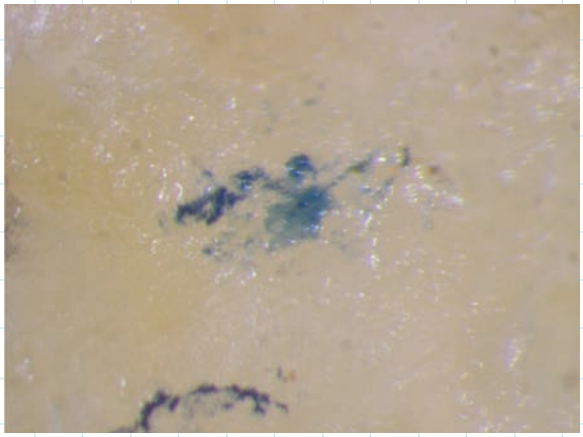


Figure 3. X-gal staining of cells reseeded on decellularized costa with calcium phosphate/DNA co-precipitate.

Conclusions

Porcine bones (femur and costa) were decellularized successfully using UHP and washing processes. The decellularized tissue would be useful in bone tissue regeneration. The decellularized bone also acted as a gene delivery/transfectioning matrice for the cells incorporated to the bone. Combining a decellularized tissue and gene delivery system is expected to be a useful technology for regenerating tissue, not only bones but also other tissues, such as blood vessels, skin, and heart muscles.

References

1. Middleton, JC, Tipton, AJ. Synthetic biodegradable polymers as orthopaedic devices, Biomaterials 21: 2335-2346 (2000).
2. Ameer, GA, Mahmood, TA, Langer, R. A biodegradable composite scaffold for cell transplantation, J. Orthop. Res. 20: 16-19 (2002).
3. Ji, Y, Ghosh, K, Shu, XZ, Li, B, Sokolov, JC, Prestwich, GD, Clark, RA, Rafailovich, MH. Electrospun three-dimensional hyaluronic acid nanofibrous scaffolds, Biomaterials 27: 3782-3792 (2006).
4. Lee, SJ, Lim, GJ, Lee, JW, Atala, A, Yoo, JJ. In vitro evaluation of a poly(lactide-co-glycolide)-collagen composite scaffold for bone regeneration, Biomaterials 27: 3466-3472 (2006).
5. Chen, G, Ushida, T, Tateishi, T. Scaffold design for tissue engineering, Macromol. Biosci. 2: 67-77 (2002).
6. Bader, A, Schilling, T, Teebken, OE, Brandes, G, Herden, T, Steinhoff, G, Haverich, A. Tissue engineering of heart valves—Human endothelial cell seeding of detergent acellularized porcine valves, Eur. J. Cardio. Thorac. Surg. 14: 279-284 (1998).
7. Grauss, RW, Hazekamp, MG, van Vliet, S, Gittenberger-de Groot, AC, DeRuiter, MC. Decellularization of rat aortic valve allografts reduces leaflet destruction and extracellular matrix remodeling, J. Thorac. Cardiov. Surg. 126: 2003-2010 (2003).
8. da Costa, FDA, Dohmen, PM, Lopes, SV, Lacerda, G, Pohl, F, Vilani, R, da Costa, MBA, Vieira, ED, Yoschi, S, Konertz, W, da Costa, IA. Comparison of cryopreserved homografts and decellularized porcine heterografts implanted in sheep, Artif. Organs 28: 366-370 (2004).
9. Fujisato, T, Minatoya, K, Yamazaki, S, Meng, Y, Niwaya, K, Kishida, A, Nakatani, T, Kitamura, S. Preparation and recellularization of tissue engineered bioscaffold for heart valve replacement, In, Mori, H, Matsuda, H, (eds), Cardiovascular Regeneration Therapies Using Tissue Engineering Approaches, Springer-Verlag, Tokyo, Japan, pp83-94 (2005).
10. Jang, JH, Shea, LD. Controllable delivery of non-viral DNA from porous scaffolds, J. Control. Release 86: 157-168 (2003).
11. Zhang, SB, Xu, YM, Wang, B, Qiao, WH, Liu, DL, Li, ZS. Cationic compounds used in lipoplexes and polyplexes for gene delivery, J. Control. Release 100: 165-180 (2004).
12. Roy, I, Mitra, S, Marita, A, Mozumdar, S. Calcium phosphate nanoparticles as non-viral vectors for target gene delivery, Int. J. Pharm. 250: 25-33 (2005). ■

Scientifically Speaking

Fluorescence Resonance Energy Transfer—A New Tool to Quantify the Stability of Antisense Oligonucleotides

By Ilva Rupenthal and Raid G. Alany
School of Pharmacy, The University of Auckland
Auckland, New Zealand

Since the late 1970s antisense oligonucleotides (AsONs) have been investigated as powerful tools for selective regulation of gene expression. Antisense drugs act by specifically binding to the target mRNA, which results in inhibition of their translation into a protein. They have already been proven efficient for the treatment of various viral infections, such as human immunodeficiency virus (HIV) type 1, hepatitis B virus, and human cytomegalovirus (CMV), and are also believed to be valuable candidates for cancer treatment. However, so far, only one antisense-based drug, Vitravene®, used for the treatment of ocular cytomegalovirus retinitis, has been approved by the FDA, and the application of the antisense strategy in clinic remains a challenge. In addition to issues involving their specificity and efficient delivery to the target side, the stability of AsONs *in vitro* and *in vivo* remains one of the major problems.

Fluorescence resonance energy transfer (FRET) is a distance-dependent physical process in which energy is transferred non-radiatively from an excited donor fluorophore to a close-by acceptor fluorophore through dipole–dipole interactions without the emission of a photon (1). Förster (1) initially became interested in this energy transfer process because of the effectiveness of photosynthesis in leaves. His first published paper on FRET in 1946 described the correct theoretical basis for the process. Two years later Förster derived a quantitative theory on non-radiative energy transfer (2). Accordingly, if a donor fluorophore is excited by incident light and an acceptor is in close proximity, the excited-state energy from the donor can be transferred to the acceptor molecule. As a result, the donor's fluorescence intensity and excited-state lifetime are reduced, and the acceptor's emission intensity increases. Förster showed that the efficiency of this process (E) depends on the inverse sixth power of the distance between donor and acceptor (Equation 1 and Figure 1). Thus, FRET can be used as an effective "molecular ruler" and is one of the few tools available to measure nanometer-scale distances (0.5–10 nm) and changes in distance, both *in vitro* and *in vivo*.

$$E = \frac{1}{1 + (R/R_0)^6}$$

Equation 1. Efficiency of energy transfer process (E); R = distance between donor and acceptor fluorophore; R_0 = Förster radius at which 50% of the energy is transferred.

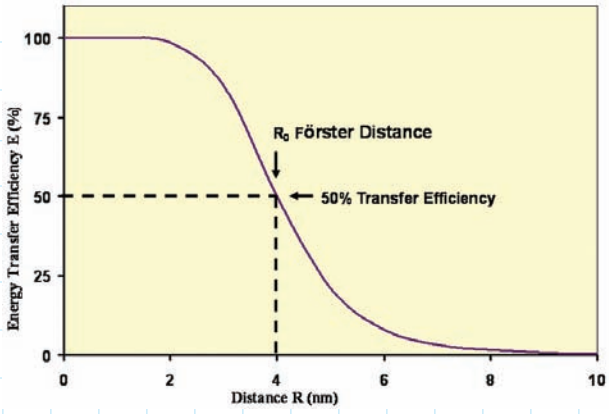


Figure 1. Exponential relationship between the transfer efficiency (E) and the distance (R) separating donor and acceptor. The efficiency rapidly increases to 100% as the separation decreases below R_0 and conversely, decreases to 0% when R is greater than R_0. Distance measurements, therefore, are only reliable when the distance between donor and acceptor lies within the Förster radius by a factor of two.

This principle can also be applied to monitor the stability of antisense oligonucleotides when tagging them with both a donor and an acceptor fluorophore. Uchiyama et al. (3) first used this approach in 1996 to investigate the integrity of oligonucleotides in solution and *in vivo*, injecting them into sea urchin eggs. Labelling 10-mer oligonucleotides with fluorescein on one end and rhodamine X on the other end, they compared the intensity ratios of red to green fluorescence over time (3). In our studies FAM (5-carboxyfluorescein) was used as a donor fluorophore and was attached to the 5′ end of a 30-mer AsON, whereas TAMRA (5-carboxytetramethyl-rhodamine) on the 3′ end acted as an acceptor molecule. Due to sufficient overlap of the FAM emission and the TAMRA excitation spectra, energy can be transferred from the donor to the acceptor molecule as long as the AsON is intact (Figure 2).

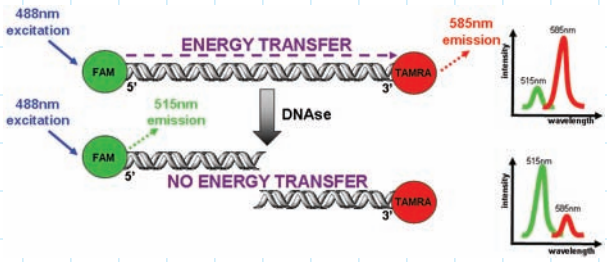


Figure 2. Principles of FRET and spectra of an intact (top) and a degraded (bottom) antisense oligonucleotide (AsON).

Several criteria must be fulfilled for FRET to occur. In addition to the overlapping emission and absorption spectra of donor and acceptor molecules, the two involved fluorophore dipoles must be properly aligned and within a distance of 1–10 nm of each other (4).

The amount of FRET is usually monitored with a fluorescence microscope comparing the fluorescence intensities of donor and acceptor. As the energy transfer results in several characteristic changes in local sample fluorescence, approaches to detect FRET include the measurement of the donor quenching in the presence of the acceptor (acceptor bleaching) or the measurement of the increased or sensitized fluorescence emission of the acceptor (sensitized emission) (Figure 3).

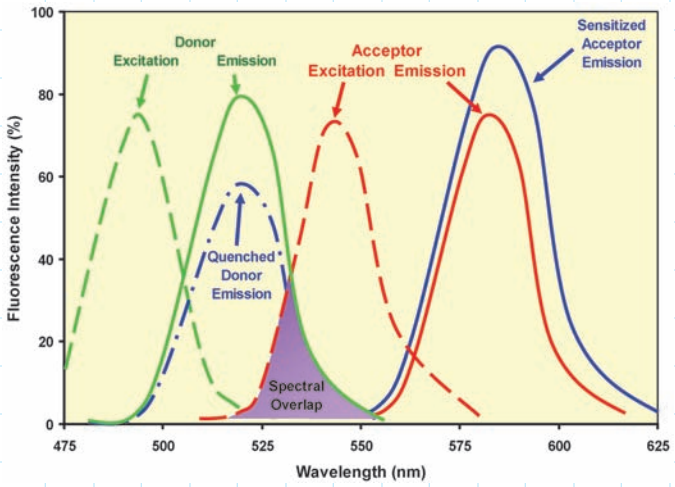


Figure 3. Spectral profiles of the donor (FAM) and acceptor (TAMRA), including quenched donor emission and sensitized acceptor emission.

Acceptor Bleaching (AB)

Measuring donor quenching in the presence of an acceptor can be achieved by comparing the donor fluorescence intensities in the same sample before and after destroying the acceptor by high laser intensity (Equation 2). If FRET was initially present, a resultant increase in donor fluorescence will occur on photobleaching of the acceptor. Since the method requires photodestruction of the acceptor fluorophore, it is incompatible with time-lapse imaging in living cells and is best applied to fixed specimens.

To assess whether this application could be used for liquid or semi-solid formulations and whether the viscosity of the formulation had any effect, calculated FRET efficiencies of the double-tagged 30-mer AsON in PBS (1 mPa·sec) and a water-in-oil microemulsion (110 mPa·sec) were compared. Results showed that the viscosity of the vehicle had an effect, as 19.38% FRET efficiency was obtained for the oligonucleotide incorporated in the more viscous water-in-oil microemulsion, whereas the PBS solution showed an efficiency of 0% (5). Therefore, this approach can only be used for highly viscous or fixed samples where Brownian motion of the molecules within the specimen is reduced.

$$FRET_{eff} = \frac{D_{post} - D_{pre}}{D_{post}} \quad for\ all \quad D_{post} > D_{pre}$$

Equation 2. FRET efficiency ($FRET_{eff}$) using the acceptor bleaching approach; D_{pre} = fluorescence intensity of the donor in the selected region of interest before the bleaching procedure; D_{post} = fluorescence intensity of the donor in the selected region of interest after the bleaching procedure.

Sensitized Emission (SE)

The most widely employed approach is sensitized emission, as it is non-destructive and can be implemented on wide-field and confocal microscopes. Thus, the sensitized fluorescence of the acceptor resulting from energy transfer from excited donor molecules is detected through an optical FRET filter set selecting acceptor emission (*B*). In practice however, this image is contaminated by directly excited fluorescence of the acceptor (*c*) and the tail of the donor emission spectrum (*b*) (Figure 3). To account for this bleed-through or crosstalk, two additional images are required: donor fluorescence during donor excitation (*A*) and acceptor fluorescence during direct acceptor excitation (*C*). Apparent FRET efficiencies are then calculated as shown in Equation 3.

$$FRET_{eff} = \frac{B - A*b - C*c}{C}$$

Equation 3. FRET efficiency ($FRET_{eff}$) using the sensitized emission approach; A, B, and C = intensities of the donor, FRET, and acceptor channels, respectively; b = B/A = donor cross-talk in the FRET image; c = B/C acceptor cross-excitation in the FRET image.

To show the applicability of this approach for AsON stability measurements, we incorporated single- and double-tagged AsONs into an *in situ* gelling carrageenan formulation and compared the calculated FRET efficiencies to the qualitative wavelength scans obtained on a confocal laser scanning microscope. In correlation with the wavelength scans, we obtained 0% FRET efficiency when mechanically mixing single-tagged probes, indicating there is no energy transfer between AsON fragments, and 27% for an intact double-tagged AsON, which was reduced back to 0% when degrading the AsON with DNAse (Figure 4) (5).

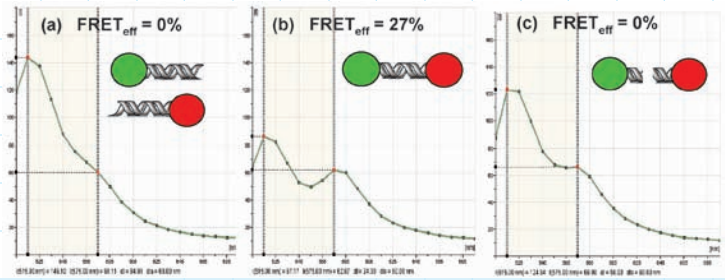


Figure 4. Wavelength scans of antisense oligonucleotide probes in an in situ *gelling carrageenan system: (A) single-tagged probes, (B) intact double-tagged probe, and (C) double-tagged probe degraded by DNAse.*

Scientifically Speaking continued on page 14

Scientifically Speaking continued from page 13

Conclusions

Although FRET is a technique that is almost 50 years old, it has recently undergone a rebirth due to advances in optical methods and instrumentation combined with the development of novel fluorescent dyes. This study shows that FRET acceptor bleaching and sensitized emission provide simple and easy-to-use tools to monitor the stability of AsONs in pharmaceutical delivery systems. However, formulation characteristics such as viscosity and pH have to be considered, and different fluorophore pairs might be necessary in some cases to meet FRET requirements.

References

1. Förster, T. Intermolecular energy migration and fluorescence. Ann. Phys. 2: 55-75 (1948).
2. Clegg, RM. The vital contributions of Perrin and Förster. Biophotonics Int. 43: 42-45 (2004).
3. Uchiyama, H, Hirano, K, Kashiwasake-Jibu, M, Taira, K. Detection of undegraded oligonucleotides *in vivo* by fluorescence resonance energy transfer: Nuclease activities in living sea urchin eggs. J. Biol. Chem. 271(1): 380-384 (1996).
4. Lakowicz, JR. Principles of Fluorescence Spectroscopy, Kluwer Academic/Plenum, New York (1999).
5. Rupenthal, ID, Green, CR, Alany, RG. FRET applications as a tool to monitor the stability of antisense oligonucleotides *in vitro*. In: 33rd Annual Meeting and Exposition of the Controlled Release Society, Vienna, Austria (2006). ■

Attention CRS Committee Chairs

Is your committee interested in meeting in Long Beach? Committees of the Controlled Release Society are invited to schedule committee meetings. Use of the committee meeting room is by reservation only. Reservations can be made now by contacting CRS Meeting Planner Leah Barna (lbarna@scisoc.org) and can also be made at the Attendee Services Desk once the Annual Meeting & Exposition has begun. The meeting room is available for use throughout the duration of the Annual Meeting & Exposition.

SPOTLIGHT:

Polymun Scientific—The Biopharmaceutical and Liposome Specialty Company

Polymun Scientific GmbH, Vienna, Austria, is a private company in founded in 1992 by Prof. Herman Katinger, a pioneer in animal cell technology. The core activity of Polymun is its innovative liposome technology, which is used to optimize the formulation of all kinds of pharmaceutically active ingredients and vaccine antigens. Another core competence of Polymun is contract development and manufacture of biopharmaceuticals, using both mammalian and microbial cell technology. Industrial applicability based on scale and price is a common focus throughout all projects and technologies. Contract manufacturing includes the preparation of IMPD and CMC documents.

Company revenues are invested in its own R&D projects and the further development of technology platforms. Polymun operates in accordance with current GLP, GMP, and GCP guidelines and holds an Austrian production license, meeting all EU requirements for drug manufacturing. Polymun employs a team of about 40 dynamic and highly qualified scientists, technologists, and support staff. Sixty percent of whom hold academic titles, mostly in natural sciences such as biotechnology, biology, or chemistry. About one-third have graduated from technical schools or colleges. With quality and reliability as a pre-requisite basis, innovation and creativity are strongly encouraged at Polymun, making it a flexible partner who is focused on the requirements of its clients.

Liposomal Formulations

Liposomes protect, transport, and release drugs at the right place and time. By this process, a reduced dose achieves better efficacy and avoids side effects through a non-invasive application. Polymun has developed a continuous ethanol injection technology for the one-step production of liposomes. The production technology is suitable for a broad range of substances formulated by passive entrapment, active loading, or membrane incorporation. The main characteristics of our technology are

- Vesicle homogeneity
- Scalability
- Aseptic process conditions
- High encapsulation rates
- Batch-to-batch consistency
- High product stability

The injection module is the heart of liposome production, where the formation of liposome takes place. Based on the principle that the ethanolic lipid solution is injected through a defined pore into a continuous flow of buffer (Figure 1), the process parameters are precisely defined. These parameters, temperature, buffer flow rate, injection pressure, pore size, and concentration and composition of lipids, determine the size of the liposomes regardless of the scale. This results in a very narrow size distribution, necessary for reliable targeting and transport characteristics (Figure 2).

As the injection module is not changed during scale-up, the process parameters are kept constant. Thus, the process yields identical results at every scale. The production of 100 L of liposome preparation takes only 40 min. Large scale also can be achieved using several injection modules in parallel. In addition, high quality of raw materials and precisely controllable process parameters guarantee high reproducibility—essential for pharmaceutical grade products.

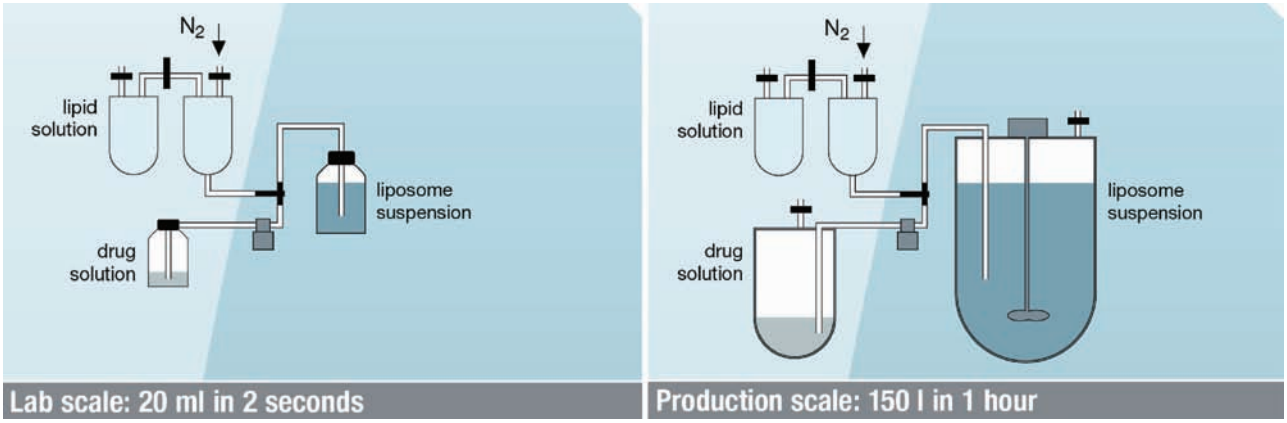


Figure 1. Production of liposomes at different scales.

Spotlight continued on page 16

Spotlight continued from page 15

Production takes place in a closed system. All components are added via sterile filtration. Subsequent concentration by cross-flow filtration is also possible. By this process residual ethanol is reduced far below the limit of 0.5% according the European Pharmacopoeia (01/2005:50400), and non-entrapped drug can be removed.

The production system can be used for different loading techniques, depending on the nature of the drug. Hydrophilic substances are passively entrapped. Amphiphilic substances are actively loaded, and hydrophobic drugs or membrane proteins are incorporated into the membrane of the liposomes. The cross-flow injection technique is a very mild procedure that allows the processing of sensitive drugs. Together with the high quality of raw materials and the narrow size distribution, the technology achieves optimal stability of the liposomes.

Using Polymun's proprietary liposome technology, several liposomal drug products and vaccines were transferred from the lab into clinical testing very quickly. The defined process criteria and aseptic conditions allow the use of development batches even in first animal trials. In addition, the versatility of this method enables production of any kind of liposome independent of a drug's nature or properties. Currently, Polymun and partners test their liposomal products in preclinical and clinical studies, ranging from the field of oligonucleotide drugs to peptide-containing liposomal vaccines to liposomal cancer therapeutics.

In February 2005 Polymun signed a license agreement with Sanochemia Pharmazeutika AG concerning the liposomal formulation of galantamine for the treatment of neuropathic pain. In October 2005, Polymun entered into a co-operation with novosom AG for the production of GMP-compliant material of novosom's Smarticles®. In January 2006, the co-operation was expanded to Micromethason, novosom's micro-dose liposomal glucocorticoid.

Biopharmaceuticals

Polymun is a developer and GMP-compliant manufacturer of biopharmaceuticals with a focus on mammalian technology. Polymun views vector, production cell line, cell banking, processes for fermentation and purification, as well as analytical methods, as parts of a networked development to achieve optimal results. Each step can be operated with protein-free

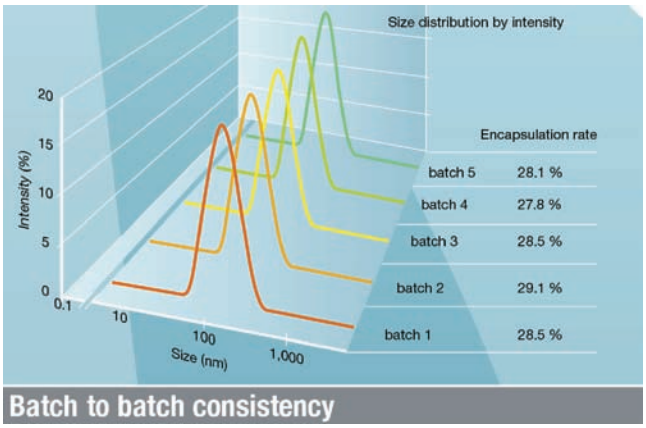


Figure 2. Size curves and encapsulation rates of reproducibility runs.

cryopreservation and cell culture media. Polymun has gathered experience in designing purification processes for proteins of all kinds—antibodies, hormones, and enzymes. A wide range of analytical methods is available that can be readily adapted to new requirements. GMP compliance and industrial applicability are central to all operations.

References

1. Wagner, A, Vorauer-Uhl, K, Kreismayr, G, Katinger, H. Enhanced protein loading into liposomes by the multiple injection technique, J. Liposome Res. 12(3): 271-283 (2002).
2. Wagner, A, Vorauer-Uhl, K, Kreismayr, G, Katinger, H. The crossflow injection technique—An improvement of the ethanol injection method. J. Liposome Res. 12(3): 259-270 (2002).
3. Wagner, A, Vorauer-Uhl, K, Katinger, H. Liposome produced in a pilot scale: Production, purification and efficiency aspects. Eur. J. Pharm. Biopharm. 54: 213-219 (2002).
4. Wagner, A, Platzgummer, M, Kreismayr, G, Quendler, H, Stiegler, G, Ferko, B, Vecera, G, Vorauer-Uhl, K, Katinger, H. GMP production of liposomes—A new industrial approach. J. Liposome Res. 16(3): 311-319 (2006).
5. Lenz, O, Dittmar, MT, Wagner, A, Ferko, B, Vorauer-Uhl, K, Stiegler, G, Weissenhorn, W. Trimeric membrane anchored gp41 inhibits HIV membrane fusion. J. Biol. Chem. 280(6): 4095-4101 (2005). ■

CeramiSphere: Micro-encapsulation and Controlled Release from Ceramic Particles

Christophe Barbé, Kim Finnie, and Linggen Kong
CeramiSphere Pty. Ltd., Menai, Australia
Website: www.ceramisphere.com
E-mail: cab@ansto.gov.au
E-mail: johan.ubbink@rdls.nestle.com

Introduction

An increasing number of applications require the production of delivery systems in particulate form. While a wide range of organic materials have been used to manufacture these capsules or particles, very few inorganic controlled release systems have found their way into industrial products. This is typically the case for ceramics that, despite a number of intrinsic advantages such as high mechanical strength, resistance to corrosion, thermal and electrical stability, bio-compatibility, and an environmentally benign nature, remain an untapped resource for the manufacture of controlled release systems. Using traditional routes, the relative difficulty in manipulating the internal microstructure of ceramics (compared with polymers), as well as high processing temperatures that are incompatible with the encapsulation of organic molecules, may explain its lack of popularity as a controlled release matrix. Both of these limitations can be overcome using sol-gel technology (1), which can be described as an inorganic, ambient temperature, polymerization technique. When combined with emulsion chemistry, it allows easy encapsulation of organic molecules inside controlled-size particles and their subsequent release (2).

Ceramisphere Technology

Sol-gel chemistry has revolutionized ceramic production by enabling ambient temperature, solution-based synthesis of metal oxides with tailorable porosity. By combining sol-gel with emulsion chemistry, it is possible to produce spherical particles with a designed microstructure based on a judicious choice of solvent/surfactant and sol-gel reaction parameters (3). By changing the solvent/surfactant combination, the particle size can be varied from 10 nm to 100 µm (Figure 1). The size of the particles is controlled by the size of the emulsion droplet, which acts as a nano-reactor for the sol-gel reaction. When an active molecule is located in the aqueous droplet, encapsulation occurs as silicon precursors polymerise to build an oxide cage around the active species. Encapsulation efficiencies for hydrophilic molecules are typically >85%, with doping levels typically in the range of 5 to 20% (wt). The release profiles can be tailored, independently of the particle size, by controlling the internal structure of the particles (pore volume, pore size, tortuosity, and surface chemistry) (Figure 2). This can be achieved easily by controlling sol-gel processing parameters such as the water/alkoxide ratio, pH, alkoxide concentration, ageing, drying time, and temperature. Hence, the release rate of the encapsulated species is controlled by adapting the structure of the internal pore network to the physico-chemical properties of the active molecule.

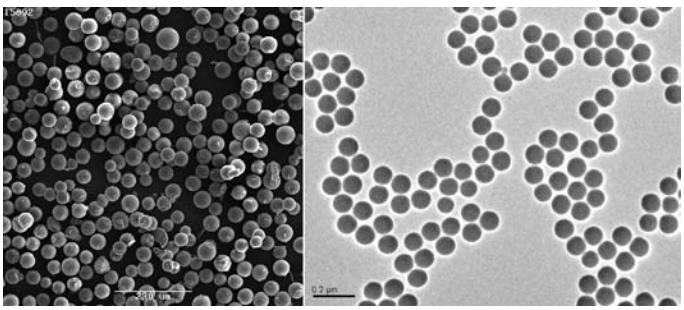


Figure 1. Micro- and nanoparticles demonstrating the range of size that can be obtained using CeramiSphere technology (scale bar: 230 µm left image and 200 nm right image).

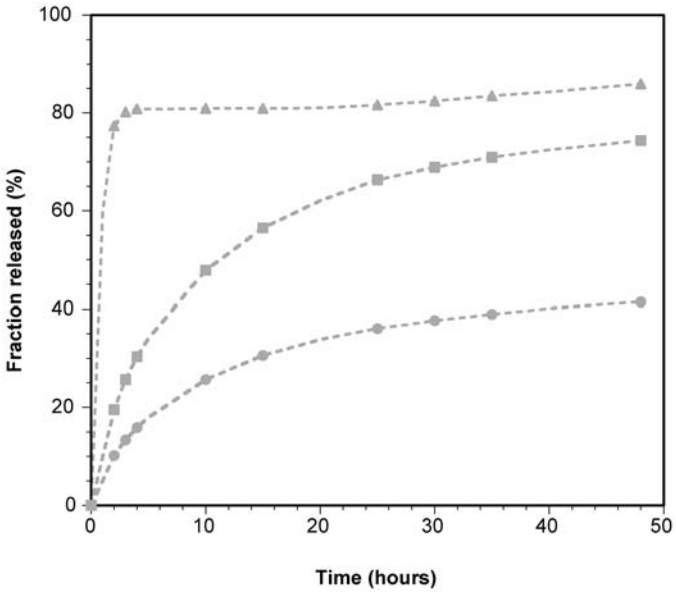


Figure 2. Release of Orange II from Ceramispheres of identical sizes but with different internal structures.

C&DP continued on page 18

C&DP continued from page 17

A Versatile Encapsulation Process

Although CeramiSphere technology was originally developed for encapsulation and controlled release of small hydrophilic molecules, we have recently expanded our technology to the encapsulation of biomolecules, poorly soluble molecules, and the production of nanoparticles with extended release capacity (multi-layered nanoparticles).

A successful biomolecule release system must be capable of delivering biomolecules at a desired rate, as well as preserving the activity of the biomolecule throughout encapsulation, storage, and release processes. CeramiSphere has developed an innovative procedure (4) by which biomolecules are entrapped in silica microspheres formed from inorganic suspensions of aqueous silica colloids. The release mechanism is diffusion of the biomolecule through the matrix pores (Figure 3). The particles are in the range of 0.5 to 10 μm in size, with pore size being optimised (2–7 nm) to provide an appropriate release rate for the biomolecule of interest (5). The process has been designed to minimise denaturation of biomolecules during encapsulation.

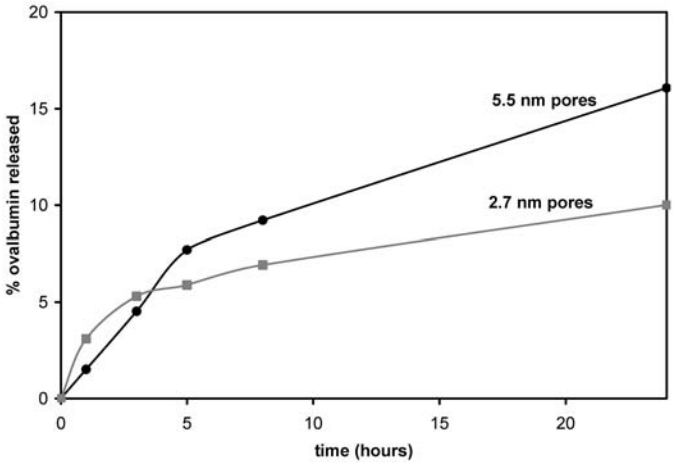


Figure 3. Release of ovalbumin (45 kDa), encapsulated in silica particles with two different pore sizes (2.7 and 5.5 nm), into phosphate buffered saline at 37°C.

The encapsulation of hydrophobic actives is a key component of their use in various industries, such as pharmaceuticals, cosmetics, and food. Several innovative methods (6,7), based on a combination of sol-gel and emulsion chemistry, have been developed by CeramiSphere to encapsulate hydrophobic molecules in the form of liquid, solution, or solids into silica micro- and nano-particles. An example of the structure of those particles is given in Figure 4. The encapsulation in silica offers good protection for sensitive molecules such as retinol against chemical attack, oxidation, or decomposition. In addition, the release rate of the molecules can be optimised for specific compounds.

The encapsulation of active pharmaceutical ingredients (API) into nanoparticles enables new routes of administration and treatment. Using room temperature sol-gel polymerisation in reverse emulsions, active pharmaceuticals can be encapsulated inside silica nanoparticles. The size of the particles can be precisely tailored from 10 to 250 nm, and the release rate can be controlled from days to months (8). The surface of the particles can be functionalised to minimise protein interaction and enhance blood circulation, for active targeting.

CeramiSphere has also developed a method for encapsulating different active molecules in separate layers of the silica nanoparticle (Figure 5) while preserving the particle monodispersity (9). This allows the production of particles with delayed-, sequential-, or pulsed-release capabilities. It also enables the encapsulation in the same particle of incompatible or reactive molecules. The ability to encapsulate various molecules in different layers in the particle also opens up a wide range of

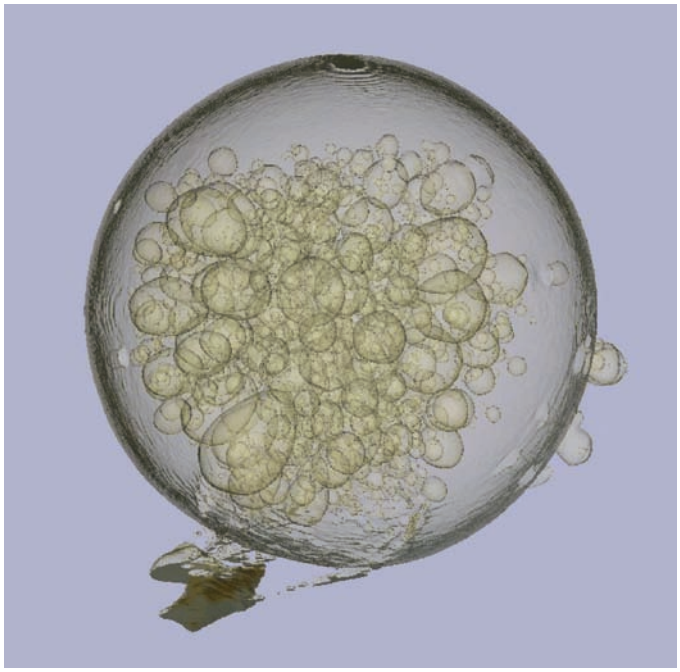


Figure 4. X-ray tomographic view of oil encapsulated inside pure silica microparticles.

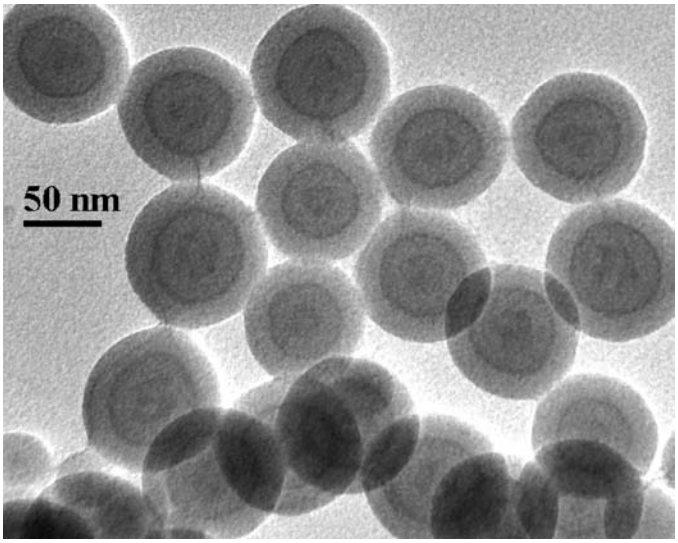


Figure 5. TEM image of layered silica nanoparticles.

novel potential applications, such as optical storage, data encryption, or security ink.

Commercialisation

CeramiSphere is seeking incorporation of our technology into the products of commercial partners, as well as potentially manufacturing and supplying our own powders. We are currently exploring, in collaboration with industrials partners, the potential for our technology to be applied in oral drug delivery, the release of biocide for building materials, and the release of corrosion inhibitors for the aircraft industry. We are also evaluating our technology with external partners for the intravenous delivery of oncology drugs, transdermal delivery, vaccine delivery, and wound-healing applications. We are also studying the scale-up of our processes from the current scale of 50- to 100-g test samples to the 1,000 ton/year scale. Thanks to our nano-reactor approach, no serious scale-up challenges are expected, and the final cost should average between US$15–20/kg for microspheres.

References

1. Brinker, CJ, Scherer, GW. Sol-Gel Science: The Physics and Chemistry of Sol-Gel Processing, Academic Press, San Diego, CA (1990).
2. Barbé, C, Bartlett, J, Kong, L, Finnie, K, Lin, HQ, Larkin, M, Calleja, S, Bush, A, Calleja, G. Silica particles: A novel drug delivery system, Adv. Mater. 16(21): 1959-1966, 2004.
3. Barbé, CJ, Bartlett, JR. Controlled release ceramic particles, compositions thereof, processes of preparation and methods of use, WO 01/62232, 2001, including US2005123611, CA2399279, MXPA02008117, and NZ520796.
4. Finnie, K, Barbé, C, Jacques, D. Controlled release of biological entities, WO2006/066317.
5. Finnie, KS, Jacques, DA, McGann, MJ, Blackford, MG, Barbé, CJ. Encapsulation and controlled release of biomolecules from silica microparticles. J. Mater. Chem. 16: 4494-4498 (2006).
6. Kong, L, Finnie, K, Barbé, C. Particles having hydrophobic materials therein, PCT/AU2006/000853.
7. Finnie, K, Kong, L, Barbé, C. Solid particles comprising a hydrophobic materials therein, PCT/AU2006/000852.
8. Kong, L, Barbé, C. Solid particles from controlled destabilisation of micro-emulsions, WO2006/050579.
9. Kong, L, Barbé, C. Multilayered nanoparticles, WO2006/084339. ■

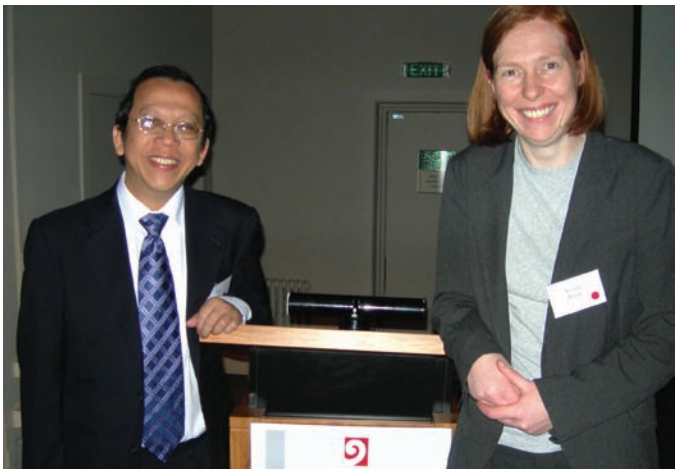
Chapter News

Formulation and Drug Delivery Conference in Dunedin

By Dr. Arlene McDowell
New Zealand's National School of Pharmacy
University of Otago, Dunedin, New Zealand

In February 2007, Prof. Ian Tucker, dean of New Zealand's National School of Pharmacy and Convener of the Formulation and Drug Delivery (FDD) Research Theme at Otago University, welcomed approximately 100 delegates to the 2-day conference held in Dunedin. Prof. Tucker spoke of the importance of a collaborative approach between groups, including biologists, immunologists, pharmaceutical scientists, and material scientists, to meet the challenges of modern drug delivery. The FDD Conference provides just such a forum for the exchange of ideas on the topic of formulation and drug delivery between people with diverse backgrounds from industry and academia.

Vaccine delivery was a major theme on the first day of the FDD Conference this year, and the keynote speaker, Dr. Yvonne Perrie, gave an elegant talk on her work using cationic liposomes to enhance the potency of Tb sub-unit vaccines. This topic was of great interest from a formulation perspective because it is complementary to research conducted at the School of Pharmacy at Otago, but also in a broader sense because Tb is present in livestock herds and wildlife in New Zealand. Yvonne travelled from Birmingham, England, to be at the conference and took the opportunity to spend a few extra days looking around Dunedin and discussing collaborations with staff at the School of Pharmacy at Otago. Yvonne is also chair of the United Kingdom & Ireland Controlled Release Society, and it was great for the New Zealand Local Chapter of CRS (NZCRS) to be able to further develop links between the two chapters.



Associate Professor Paul Heng and keynote speaker Dr. Yvonne Perrie at the 2007 Formulation and Drug Delivery Research Theme and New Zealand Local Chapter Conference.

Chapter News continued on page 20

Chapter News continued from page 19

The NZCRS is a co-organiser of the FDD Conference, and we were very pleased to have Assoc. Prof. Paul Heng (National University of Singapore) as this year's NZCRS invited speaker. On the second day of the conference, the challenges of taking laboratory discoveries through to products were considered by the speakers. Paul introduced this part of the program with a lively and stimulating talk about tablet coating that illustrated very nicely how the research conducted by pharmaceutical scientists can help to improve pharmaceutical production. I know that many of our postgraduate students also valued the opportunity to discuss their work individually with Paul.

Other keynote speakers who we were fortunate to have present at the conference included Firoz Ghazali, technical manager, Douglas Pharmaceuticals, Fiji; Dr. Michael Rathbone, general manager and director of research, InterAg, Hamilton; Dr. Martin Wunderlich, a senior scientist at InterAg; and Dr. Karen Krauel, lecturer, Massey University, Wellington.

Another highlight of the conference for me was a "Soapbox" talk by Prof. Frank Griffin (Department of Microbiology and Immunology, University of Otago) who gave a thought-provoking talk on the importance of choosing relevant animal species as experimental models (Are rats and mice really that similar to humans?) and measuring parameters that will give useful information—not just measuring something because you can!

This year we introduced co-chairs for some of the sessions. The idea behind this was to give postgrads the opportunity to lead a conference session, with the support of someone who had more experience. Graduate student Ruedeeporn (Sun) Tantipolphan chaired a session with Prof. Ian Tucker and graduate student Alexandra Kafka chaired a session with myself. Alex is also the postgraduate representative on the Steering Committee of the FDD. Both are to be complimented on the fantastic jobs they did.

The NZCRS again sponsored prizes for the Best Oral Presentation by a postgraduate student at the FDD Conference. The 2007 winner was Julia Myschik (School of Pharmacy, University of Otago), and the joint runners-up were Norman Chieng (School of Pharmacy, University of Otago) and Sarah Wilson (Department of Microbiology and Immunology, University of Otago). As in previous years, the standard of presentation and the science they spoke about was very high. In addition to the recognition associated with the award, the NZCRS provides financial support for the winning student to present their work at the CRS Annual Meeting. This year Julia is very excited to be able to attend the CRS meeting in Long Beach, California.

Winner of the NZCRS Best Oral Presentation, Julia Myschik, with NZCRS President Prof. Thomas Rades (above) and joint runners-up Sarah Wilson and Norman Chieng.

Next year will be a milestone for the FDD as we celebrate a decade of this successful conference. We plan to make it bigger and better than ever. I encourage you to keep an eye out for information on our FDD Conference and extend a warm invitation to come and find out first-hand about the research going on in the New Zealand region. ■

Chapter News

Controlled Release Society—Indian Chapter Organises 7th International Symposium in Mumbai

Dr. (Mrs.) K. K. Singh
Secretary CRS-Indian Chapter
SNDT Women's University, Mumbai, India

The Controlled Release Society-Indian Chapter organized the 7th International Symposium on Advances in Technology & Business Potential of New Drug Delivery Systems on February 13 and 14, 2007, at the ITC Hotel Grand Maratha Sheraton & Towers in Mumbai.

This international meeting was inaugurated by Mr. Rajesh Jain, joint managing director of Panacea Biotech Limited, who also delivered an inaugural lecture on the theme of the symposium. Mr. Ajit Singh, president of the CRS-Indian Chapter and chair of ACG-Worldwide, welcomed the guests and delegates, while Dr. Amarjit Singh, vice president of the CRS-Indian Chapter and president (R&D) of Panacea Biotech Ltd., told the audience about the mission of the CRS-Indian Chapter. Dr. (Mrs.) K. K. Singh, secretary of the CRS-Indian Chapter and professor in pharmaceutics SNDT Women's University, presented floral bouquets to the dignitaries.

The guest of honour, Dr. Tadanori Mizoguchi, senior advisor for international affairs at Tokyo University of Science, expressed the need for cooperation and collaboration between institutions in India and Japan in the development of NDDS for infectious diseases in Asian countries.

The main theme of symposium was new developments in the field of new drug delivery systems, with a special focus on design strategies for drug delivery; targeted, cellular and bioadhesive drug delivery; drug transporters in drug delivery; recent developments; and IPR issues. There was also a special session on excipients showcasing where three companies (Noveon, Asahi-Kasei, and International Specialty Products) have focused their core technologies, capabilities, and products.

The world-renowned scientists who presented discussions during the 2-day symposium included

- Prof. Leslie Benet, "Prediction of Drug Absorption and Elimination Using Biopharmaceutics Classification Systems"
- Prof. Vladimir P. Torchilin, "Pharmaceutical Nanocarriers for Cancer Therapy and Imaging"
- Prof. Tsuneji Nagai, "Drug Targeting to Liver Using Liposomes Containing Soybean Derived Sterylglucoside"
- Prof. Kimiko Makino, "Pulmonary Drug Delivery System for Treatment of Tuberculosis"
- Prof. Sevda Senel, "Oral Mucosal Drug Delivery and Therapy"
- Prof. Carla Caramella, "Systems Based on Chitosans and Chitosan Derivatives for Improving Transmucosal Drug Delivery"
- Prof. Rainer Muller, "Drug Nanocrystals: State of Art and Future Development"
- Dr. V. Venkateswarlu, "Lipid Nanoparticle Drug Delivery Systems"
- Prof. Graham Buckton, "Physical Characterization of Materials Bringing Value for Drug Delivery"
- Dr. Mark Pohl, "Cost-Effective Ways to Resolve IPR Disputes

Student and academic researchers presented around 135 posters, reflecting the high calibre of research in India, on the theme of the symposium. More than 350 delegates, including 10 from abroad, from industry, academia, and students all over India participated in the event and interacted with the faculty members and poster presenters. The symposium provided a platform for interaction between scientists and technologists from industry, universities, and institutes; business development personnel; regulatory authorities; and decision makers from industry.

The Line Between Veterinary and Human Controlled Drug Delivery

By Dr. Craig R. Bunt
Senior Scientist, AgResearch
Christchurch, New Zealand

This is a short article that looks at Veterinary and Human Controlled Release and the flow of technologies.

Introduction

There is perhaps a perception that veterinary controlled drug delivery doesn't push the scientific boundaries, is rather simple and crude, has limited potential in a low margin market, and quality (e.g., GMP) is easier to meet. Two of these statements, "veterinary controlled drug delivery doesn't push the scientific boundaries" and "veterinary controlled drug delivery is rather simple and crude," will be the focus of this article. In terms of the veterinary drug delivery markets, the U.S. intra-mammary antibiotic market is estimated at about US$70 million, while the worldwide losses to the dairy industry due to mastitis is estimated at $35 billion (1), suggesting perhaps that there are many unmet needs. Of the $11 billion animal health market, drug delivery products make up $4 billion, and the companion animal market makes up $1.6 billion. The products used to treat mastitis or any other conditions in food-producing animals in all major markets must be produced according GMP codes (11,12) identical, or almost identical, to those used for human pharmaceuticals.

Veterinary to Human?

Examples of veterinary controlled drug delivery technologies that have moved into or contributed to the human pharmaceutical field are quite common. Akin to the chicken and egg scenario, "What came first the veterinary or the human application?" is an often difficult question to answer. Sourcing research published before the introduction of electronic journals or databases is difficult and frustrating at times and means that much of the early work has not been reported widely. Identifying when and where a controlled drug delivery technology first emerged often requires personal communication with those involved in the early days of a technology's research and development.

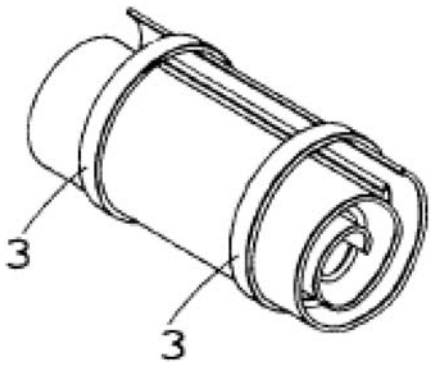


Figure 1. A rumen device (Griffin and Brewer).

Gastro-retentive dosage forms (GRDF) for humans have been the focus of much interest recently (6), yet while for both the veterinary and human fields the challenges and solutions have been similar, the veterinary filed predates the human by 10–20 years. Early solutions to rumen retention investigated devices that relied on high density or a change in geometry following administration to a form that could not pass back up the oesophagus, with both approaches achieving a similar level of success. To date there are more than 30 products on the market using either method to provide long-term gastro retention in the rumen. High density, however, cannot be exploited to provide long-term retention in humans; rather, low density (floating) or geometry offer the most promise. Devices for animals that can be configured to a shape for swallowing or administration that upon contact with rumen fluids expand or unroll (Figure 1) are common in the patent literature (3,4).

One such product (Figure 2) for the delivery of morantel is based on this approach. The Paratect Flex™ (approved in the United States in 1991) consists of a tri-laminated, perforated, plastic sheet. Similar approaches have been investigated for human gastro retention, with the Accordion Pill™ an example of a recent advance. The pill consists of a laminate of drug containing and form providing layers that are folded into an accordion-like arrangement and filled in a gelatine capsule.

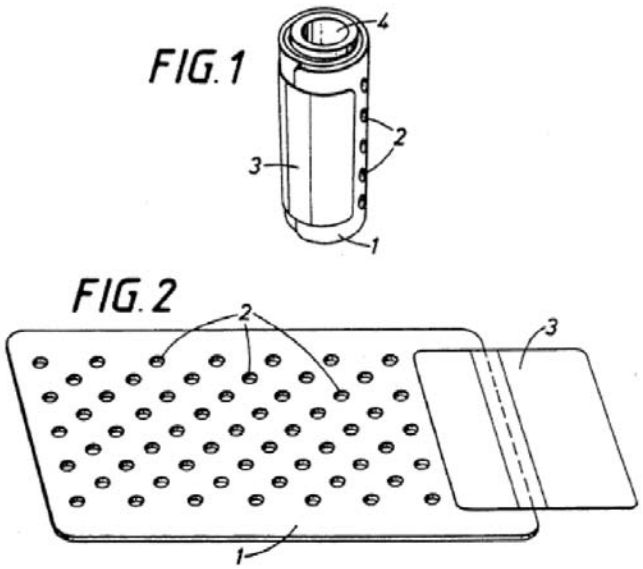


Figure 2. The Paratect Flex™: above, administration form; and below, configuration taken upon exposure to rumen fluids (Grims haw and Weatherley).

Upon administration and contact with stomach contents, the capsule dissolves and releases the accordion pill, which unfolds to its original shape.

Another area of veterinary controlled drug delivery that somewhat predates human controlled drug delivery is the use of so called patch-less transdermal delivery. The solution to the question "Where do you put a patch on a hairy animal?" was answered simply by avoiding patches. The use of ivermectin to treat external and internal parasites emerged in the late 1970s (7), while it's use for treating internal parasites by external application began in the early 1990s with the introduction of Ivomec® pour-on. The use of externally applied solutions to systemically deliver pharmaceutical agents to humans has been evaluated since the early 2000s (5) and extensively by Acrux of Melbourne, Australia.

Human and Veterinary?

Sometimes a new controlled drug delivery technology enters the veterinary and human fields almost simultaneously. Atrigel™ is a depot-forming injectable technology that employs a solution of poly(lactide-co-glycolide) and drug dissolved in an organic solvent. Upon introduction into a biological system, water causes the polymer to precipitate, thereby encapsulating or trapping the drug at the injection site (9). Eligard™ for the treatment of prostate cancer and Doxirobe™ for the treatment of canine periodontal disease were approved by the FDA in January 2002 and 1997, respectively.

For veterinary pharmaceutics for food-producing animals, it might appear that there is a case for claiming that controlled drug delivery technologies, while not necessarily crossing directly over, do lend support or provide significant insight and direction for human applications and that in general the flow of technology is from veterinary to human. This certainly is the case for gastro retention, where the examples in the veterinary field far outnumber those in the human. There are some complex technologies where there appears to not be a similar human example, delivering a regimen of multiple drugs with different dosing rates from a single administration, such as the electronically controlled intravaginal intelligent breeding device for cattle (8).

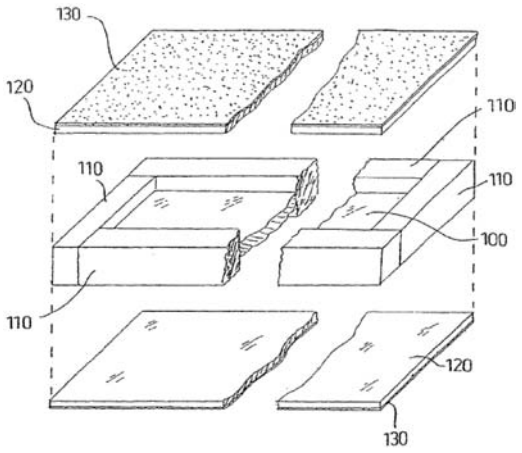


Figure 3. Laminate structure of the Accordion Pill™ (Friedman et al.).

Human to Veterinary?

One area of veterinary controlled drug delivery that is very similar to human controlled drug delivery, raising similar emotions and showing similar market trends to the human controlled drug delivery field, is the companion animal market, especially when compared with paediatric medicines. And, it is this field where the flow of technologies often goes in reverse, from human to veterinary. As the human population ages, with development focused on congestive heart failure and other diseases, many therapies have been borrowed or directly crossed over from human to veterinary medicine (Vaughn, 2005). The challenge associated with taste masking and stability of omeprazole suspensions for children is very similar for the veterinary field, with Merial's GastroGard formulated as a cinnamon-flavoured paste for horses developed to address these issues. There has yet to be developed an oral paste or suspension for humans, so once again perhaps the technology will flow from the veterinary to the human field?

References

1. Bhattarai1, S, Rathbone, M, Bunt, C, and Alany, R. *In vitro* release and teat retention of novel *in situ* gelling intramammary delivery systems, Proc. Int. Symp. Control. Release Bioactive Mat. 33 (2006).
2. Friedman, M, Klausner, E, Lavy, E, Hoffman, A. Gastroretentive controlled release pharmaceutical dosage forms, US Patent 6685962 (2004)
3. Griffin, GJL, Brewer, MD. Sustained drug release device, US Patent 4268497 (1981).
4. Grimshaw, WTR, Weatherley, AJ. Veterinary devices, US Patent 4994275 (1991).
5. Humberstone, AJ, Evans, AM, Nation, RL, MacLennan, AH. Comparison of pharmacokinetics and tolerability following application of an Estraderm 50® patch or a novel Estradiol Metered-Dose Transdermal Spray (MDTS®), NAMS 2002 Estradiol (2002).
6. Klausner, EA, Lavy, E, Friedman, M, and Hoffmann, A. Expandable gastroretentive dosage forms, J. Control. Release, 90: 143-162 (2003).
7. O'Brien, DJ. Treatment of psoroptic mange with reference to epidemiology and history, Vet. Parasitol. 83: 177-185 (1999).
8. Rathbone, MJ, Macmillan, KL, Bunt, CR, Burggraaf, S. Conceptual and commercially available intravaginal veterinary drug delivery systems, Adv. Drug Deliv. Rev., 28: 363-392 (1997).
9. Sartor, O. Eligard® 6: A new form of treatment for prostate cancer, Eur. Urol. Suppl., 5(18): 905-910 (2006).
10. Vaughn, S. Veterinary medicine: Future challenges and directions, In: 14th Biennial Symposium of the American Academy of Veterinary Pharmacology and Therapeutics. Published online at www.ivis.org, American Academy of Veterinary Pharmacology and Therapeutics, Ithaca, NY (2005).
11. FDA. www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm, visited April 13, 2007.
12. NZFSA. www.nzfsa.govt.nz/acvm/publications/other-standards/manufacturing-guideline.pdf visited, April 13, 2007. ■

Controlled Release Education, Research, and Industry In Australia

By Dr. Ben J. Boyd
Victorian College of Pharmacy
Monash University, Melbourne, Australia

This is the fourth installment in a series of short education articles that look at controlled release education, research, and industry initiatives in various parts of the world.

Pharmacy and Formulation Science Education in Australia
The tertiary education sector in Australia is led by the so called "Group of Eight" (Go8) universities, comprising the Universities of Adelaide, Melbourne, New South Wales, Queensland, Sydney, Western Australia, the Australian National University, and Monash University. Of these institutions, only Monash (Figure 1, [1]) and the Universities of Sydney (Figure 1 [2]) and Queensland (Figure 1 [3]) offer full undergraduate degrees from which students obtain a Bachelor of Pharmacy (B.Pharm.) degree. Additional non-Go8 institutions that offer a B. Pharm. degree are the Universities of South Australia (Figure 1 [4]) and Tasmania (Figure 1 [5]), Latrobe University (Victoria) (Figure 1 [6]), Charles Sturt University (New South Wales) (Figure 1 [7]), James Cook University (Queensland) (Figure 1 [8]), and Curtin University of Technology (Western Australia) (Figure 1 [9]). The undergraduate courses are typical for 4-year undergraduate degrees, with direct access to the pre-registration year on completion of the B. Pharm. Only Monash offers a combined degree with pharmacy, in which a double degree in pharmacy and economics can be read.

Figure 1. Australian Universities at which Bachelor of Pharmacy undergraduate degrees are currently offered: [1] Monash University, [2] University of Sydney, [3] University of Queensland, [4] University of South Australia, [5] University of Tasmania, [6] Latrobe University, [7] Charles Sturt University, [8] James Cook University, and [9] Curtin University of Technology.

A recent Australian Government inquiry into skills shortages in science-based industries recognised a critical shortage of graduates with formal skills in formulation, product development, GXP, and regulatory issues, particularly in the pharmaceutical industry (1). These roles traditionally have been filled by either chemists or pharmacists, but neither has the necessary formal university training in relevant issues to be competent in these roles in a short period of time. The report coincided with the introduction of a new degree course at Monash University, the Bachelor of Formulation Science and later Bachelor of Pharmaceutical Science (B.Pharm.Sci.) in 2007, with the intent of providing graduates with the necessary skills for employment across a range of industries, including pharmaceutical, cosmetics, food, surface coatings, and specialty chemicals, to name a few. In the five years that the degree course has been in operation, all graduates have either gained employment directly from their degree in the formulation field or are undertaking postgraduate research programs. From 2007 forward, the B.Pharm.Sci. degree will be offered as a double degree in conjunction with a Bachelor of Engineering degree.

RMIT University (a former technical college based in Melbourne, Australia) offers a Bachelor of Applied Science-Pharmaceutical Sciences that focuses on drug discovery. There is also a Bachelor of Pharmaceutical Sciences degree course offered through Griffith University in Queensland that operates as a pre-pharmacy degree for subsequent completion of a Masters in Pharmacy to permit access to the pre-registration year.

The formal training of pharmacists in Australia has traditionally adopted the philosophy of training students in enabling science and supplementing this foundation with specialty training in the

clinical aspects of hospital and community pharmacy. However, Australia has a growing population, and rapid urban sprawl has caused a high demand for community pharmacists. This situation has led to a number of institutions offering a Masters in Pharmacy, providing sufficient background in clinical aspects of pharmacy, for their graduates to obtain pre-registration qualifications. Consequently, there is currently a total of 16 degree courses across Australia (including the nine listed above) for a population of approximately 20 million people, compared with fewer pharmacy schools in the United Kingdom, for a population of >60 million people. As the market for registered pharmacists is saturated over the next few years, the future of many of these new smaller schools will be uncertain.

Controlled Release Education
Despite Australia's relatively strong controlled release (CR) research community, there are no formal undergraduate units exclusively comprising pharmaceutical CR technologies in Australia. However, many aspects of CR are often addressed under pharmaceutical chemistry, applied biopharmaceutics, and veterinary dosage forms.

The University of Melbourne offers an undergraduate unit in Controlled Release Fertilizers as part of their undergraduate Bachelor of Applied Science—Institute of Land and Food Resources. A number of Chemical Engineering degree courses also offer units in microencapsulation technologies. The University of Sydney offers Controlled Release Systems as an elective unit in the honours year.

Swinburne University's undergraduate courses in biotechnology and biochemistry involve a number of topics relating to controlled degradation of polymers and/or characterisation of colloidal drug delivery systems. These include polymer degradation in relation to tissue engineering, biodegradable polymers, and the colloidal characterisation (zeta potential and cryogenic scanning electron microscopy) of drug laden liposomes.

At the Victorian College of Pharmacy–Monash University, issues pertaining to controlled release dosage forms are covered in the third year of the Bachelor of Pharmacy degree, including microencapsulation, polymer coated tablets, osmotic-controlled systems, and parenteral controlled release (liposomes and pegylated liposomes). The Bachelor of Pharmaceutical Science provides a full semester on drug delivery and biopharmaceutics that addresses many aspects of controlled release.

Controlled Release Research in Australia
Academic and Government (Commonwealth Scientific Industrial Research Organization [CSIRO]). Research in CR for pharmaceutical applications is strong in the Department of Pharmaceutics at the Victorian College of Pharmacy. Prof. Bill Charman (winner of the 2006 International Career Achievement Award in Oral Drug Delivery from Eurand and the Controlled Release Society), Assoc. Prof. Chris Porter and Dr. Ben Boyd conduct research into lipid-based delivery systems. Dr. Boyd also conducts a number of research activities aimed at understanding the potential of liquid crystalline systems as delivery systems for both pharmaceutical and agricultural applications. Prof. Peter Stewart investigates the role of controlling dissolution as a means to enhance GIT drug delivery and particle–particle interactions and their impact on pulmonary delivery. Profs. Barrie Finnin and Barry Reed and Dr. Joseph Niccolazzo have contributed greatly to understanding in the field of transdermal and buccal drug delivery.

Dr. Gareth Forde (2) in the Department of Chemical Engineering at Monash University conducts research into encapsulated proteins and DNA for use as vaccines. Prof. Frank Caruso (3) has been developing drug delivery systems based on layer-by-layer polymer deposition around a central drug core for targeting and controlled release.

Prof. Clive Prestidge (4) at the Ian Wark Research Institute (University of South Australia) has been working on the use of porous silicon powders and wafers as a means of controlled release of peptides and proteins. At CSIRO Molecular Health Technologies, Dr. Patrick Hartley (5) is developing functionalised liquid crystalline systems for the controlled uptake of toxins such as ricin. This work complements that of Prof. Calum Drummond at CMHT who is developing amphiphilic prodrugs that self assemble into liquid crystalline matrices for controlled release applications. Drs. Leo Le Jambre and Keith Ellis and Ms. Kerri Tyrell at CSIRO Livestock Industries research facilities near Armidale in NSW have produced a single controlled release formulation for effective long-term protection against the damaging intestinal worm, *Haemonchus contortus*, incorporating pulsed-release levamisole in a formulation with ivermectin (6).

Swinburne University has several industry partners in the area of drug encapsulation and delivery systems. Central to such systems are the controlled degradation of polymeric films and/or the characterisation of colloidal formulations (e.g., liposomes) in terms of their particle size, stability, and drug carrying capacity. Assoc. Prof. Ian Harding, Adj. Assoc. Prof. Bob Laslett, and Dr. Ranjith Jayasekara are key staff involved in these areas. Swinburne also has expertise in the biodegradation of polymers.

Researchers across the Schools of Pharmacy, Medicine, Molecular and Microbial Science, Engineering, and Land and Food Science at the University of Queensland use controlled release technologies to improve the formulation and delivery of peptides, proteins (including vaccines) and polynucleotides (DNA, RNAi), tissue engineering, microencapsulation, and transdermal drug delivery. A recent initiative at the University of Queensland has been the establishment of the Australian Institute for Bioengineering and Nanotechnology (AIBN), which brings together engineers, chemists, biologists, and computational scientists to conduct world-class research to advance knowledge in the rapidly developing fields of nanotechnology and bioengineering to benefit human health, manufacturing, information technology, and the environment (7). In particular, Dr. Nigel Davies conducts research into polymeric (micro- and nanoparticles) and lipid (liposomes, modified-liposomes, and ISCOM-like structures) systems for

From the Education Committee continued on page 26

From the Education Committee continued from page 25

delivery of vaccine antigens incorporating immuno-modulators and adjuvants.

Assoc. Prof. Gavin Ash at Charles Sturt University in Wagga Wagga, New South Wales, investigates the use of microencapsulation to improve the efficacy and shelf life of biocontrol agents, including both bacteria and fungi, for agricultural applications (8). In particular the use of microcapsules containing mycelium as an "artificial spore" for fungi that have poor spore production and microcapsules as a delivery mechanism for bacteria to improve application technology in the soil environment are being evaluated.

Industry

Although large pharmaceutical companies conduct very little research in Australia, Australia has a large number of small biotech companies, many of which are looking to use CR dose forms for candidate drugs with short half lives or that have stability issues. A few examples are highlighted below.

- Clinuvel Pharmaceuticals (formerly know as Epitan) has begun a trial in Adelaide of a controlled release pellet form of CUV1647, a drug that stimulates photoprotective melanin production in skin.
- Acrux Ltd., located in Melbourne and originally established by researchers at the Victorian College of Pharmacy, specializes in the use of transdermal delivery of hormonal and analgesic compounds using a rapid drying formulation approach and proprietary application and enhancer technologies.
- CeramiSphere Pty. Ltd. is a wholly owned subsidiary of the Australian Nuclear Science and Technology Organisation (ANSTO is a federal government research organisation located in Sydney) that is commercialising a patented technology aimed at providing encapsulation and controlled release of active molecules for a variety of applications, including drug delivery, cosmeceuticals, and speciality chemicals using nano- and micron-sized, biocompatible and inert ceramic spheres.
- PolyNovo, based in Melbourne, is a CSIRO spin-off company focused on developing a novel family of biodegradable polymers, NovoSorb™, for use in medical devices.
- Phosphagenics, also based in Melbourne, is developing transdermal drug carrier systems based on patented phosphorylated molecules that enhance transport within the dermis.

Summary

Despite the relatively strong CR research base in Australia, there is no coordinated approach to undergraduate or postgraduate training in CR. The future establishment of a chapter of the Controlled Release Society was recently discussed at the Australasian Association of Pharmaceutical Scientists meeting in Adelaide in December 2006. The formation of such a network of CR researchers would be a favourable step toward an increased focus on training researchers in controlled release technologies and opportunities as a means to boost Australia's profile, research output, and industry success in developing new CR technologies in the future.

General References

1. Pharmaceuticals Section–Department of Industry Tourism and Resources. Ideas for Development. The report of stakeholder workshops to develop Australia's capabilities in preclinical and scale-up manufacturing for the pharmaceutical industry. Pharmaceuticals Section–Department of Industry Tourism and Resources, Canberra, Australia (2004).
2. Monash University. www.eng.monash.edu.au/chemeng/research/bel/index.html.
3. Johnston, APR, Cortez, C, Angelatos, AS, Caruso, F. Layer-by-layer engineered capsules and their applications, Curr. Opin. Colloid Interface Sci. 11: 203-209 (2006).
4. Prestidge, CA, Barnes, TJ, Mierczynska-Vasilev, A, Kempson, I, Peddie, F, Lau, CH, Barnett, C. Peptide and protein loading into porous silicon wafers, Phys. Stat. Sol. In press.
5. Hartley, PG, Alderton, MR, Dawson, RM, Wells, D. Ricin antitoxins based on lyotropic mesophases containing galactose amphiphiles, Bioconj. Chem. 18: 152-159 (2007).
6. CSIRO. www.csiro.au/news/ps21b.html.
7. Ash, G. www.csu.edu.au/faculty/sciagr/sag/admin/ash.html.
8. Australian Institute for Bioengineering and Nanotechnology, University of Queensland. www.aibn.uq.edu.au. ■

What's on Board

By Randall Mrsny
CRS President

2007–2008 CRS Election Results

The results of the current CRS elections have been finalized. Regretfully, not all of the outstanding candidates for 2007 could be elected. I use the term regretfully in that I realize such an outcome can act to de-motivate someone to run for office or become involved in the Society in the future. The wishes of the CRS Board are that the recent candidates do not look at these results in any way other than that they were identified by the Society's Nominations Committee as being exceptional individuals whose skills and talents were recognized as those desired by the Society for its leadership. For that reason, I feel I can speak for all of the Board members when I say that I am hoping all of the recent and future candidates will look at elections as a path to CRS involvement and leadership in the future. Please thank these 2007 candidates for their willingness to run and serve if elected.

Farid Dorkoosh
Hamid Ghandehari
Ick Chan Kwon
Karsten Maeder
Ram Mahato
Dody Reimer
W. Mark Saltzman
Soon Hong Yuk

The entire CRS membership and Board thank the following newly elected Board members for running and the efforts they will put forth in the future to maintain the CRS as the premier society for the international dissemination of information involving controlled release technologies. Welcome aboard!

Vice President – Diane Burgess
Scientific Secretary – Ijeoma Uchegbu
Treasurer – Arthur Tipton
Member-at-Large – Elka Touitou
Board of Scientific Advisors:
- Joke Bouwstra
- Kam Leong
- Claudia Leopold
- Mariko Morishita
- Patrick Sinko

Thanks also go to the CRS membership for taking the time to vote. Your voice is appreciated and needed for the Society to grow. ■

Welcome New Members

Celal Albayrak
Helen Baldascini
Michael J. Bassett
Arindam Basu Sarkar
Upkar Bhardwaj
Shiladitya Bhattacharya
Mayank D. Bhavsar
Iulian M. Bobe
Mark P. Borgman
Kurt E. Breitenkamp
Claudia Camellini
Deborah H. Charych
Sibao Chen
WeiQiang Cheng
Wilson Cheng
Norman H. L. Chieng
Trinidad Coll Zapata
Richard A. Compton
Nipun Davar
Goril Eide Flaten
Ulla M. Elofsson
William Good
Alex Goraltchouk
Anja Graf
Lauren Heading
Emmanuel Heinrich
Sarah M. Hook
Michael E. Houghton
Michelle Hu
Min Huang
Kenjiro Ikuta
Alfredo Inatti
Kazuo Ishii
Amal N. Ismail
Paras Jain
Kevin Jiang
Thomas H. Jozefiak
Tatiana Kabanova
Amit A. Kale
Vinayagam Kannan
Tianya Ke
Hyun D. Kim
Amit Kokate
Wei Kong
Phanidhara R. Kotamraj
Upendra D. Kulkarni
Rajkumar Kumarathasan
Subhas C. Kundu
Carol M. Laird
Karla J. LaPorte
Hyukjin Lee
Jun H. Lee
So-Young Lee
Andrew L. Loxley
Barbara Lueckel
Abdullh Al Mahmud
Shirui Mao
Jane L. McDowell
Aaron M. Mendes
Alpesh Mistry
Sarita Mittal
Hong M. Moulton
Rouslan I. Moustafine
Shohre Nabahi
Seshadri Neervannan
Kaori Nishizaki
Richard L. Norton
Steven L. O'Donnell
Esra Ogru
Anitha Palamakula
Pankaj V. Paranjpe
Atul Patel
Yogesh B. Patil
Louk A. R. M. Pechtold
Rosa Pereira
Pablo A. Rachitzky
Jani Kristian Räty
Pilar Redondo
Steven Ren
Thomas B. L. Riisager
Meyer R. Rosen
Ruma P. Sarkar
Atsushi Shiotani
Kevin N. Sill
Celio Lopes Silva
Eric A. Simone
Marina Sokolinsky
Grazia Stagni
Sudeep K. Takhar
David H. Thompson
Stephanie G. Tremonte
Sunita I. Tufekcic
Vinay S. Vellingkar
Nai Fang Wang
Ya-Jane Wang
Xiangchun Yin
Haiyan Zhang

Patent Watch

Transdermal Update

P. Batheja and B. Michniak
Ernest Mario School of Pharmacy
Rutgers-The State University of New Jersey, New Brunswick, NJ
and A. Kydonieus
Samos Therapeutics, Inc., Kendall Park, NJ

We searched the literature for patents and patent applications published during calendar year 2006, and we discovered 281 such publications. Of these, 39 were issued US patents and 82 US patent applications. There were also 65 World patents (WO), 87 European patents (EP) and 8 Japanese patent publications. It should be noted that many of these patents are counted more than once, since a patent application can be filed in the US, WO, and EP patent systems at the same time. In this update we only review the US patents. Of the 39 US patents, 14 pertain to electromechanically enhanced delivery and 25 to passive diffusion, including chemical enhancement. Some of the most pertinent patents are summarized below.

There were also several important announcements of commercial interest during the year, including the introduction of several new products.

In February 2006 the FDA granted approval to the EMSAM® patch for major depressive disorder in adults. The product is manufactured by Mylan Technologies for Somerset Pharmaceuticals and is marketed by Bristol-Myers Squibb for once per day application. The patch contains the antidepressant selegiline, belonging to the MAOI class of agents. These agents work through potentiation of monoamine neurotransmitter activity in the brain by inhibiting the MAO enzyme.

Also in February, Schwarz Pharma obtained approval from the European Commission for its Neupro® patch and a few weeks later approval to market from the FDA. The patch contains the active ingredient rotigotine, and it is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease. Rotigotine is a non-ergolinic dopamine receptor-agonist, and the patch formulation is designed for once per day application. The patch is also being developed for treating patients with advanced Parkinson's disease, as well as for treating restless leg syndrome.

In April, the FDA approved the Daytrana patch to treat attention deficit hyperactivity disorder (ADHD) in children ages 6–12. ADHD is a neurologic brain disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity. Daytrana contains the active ingredient methylphenidate, a schedule II controlled substance. The patch is marketed by Shire Pharmaceuticals and manufactured by Noven Pharmaceuticals.

In May, the FDA approved the IONSYS iontophoretic patch for management of acute moderate-to-severe post-operative pain, for use by adults, in hospital settings. IONSYS, which contains the active ingredient fentanyl hydrochloride, was also approved by the European Commission in January 2006. The patch is designed to adhere to the patient's arm, and the system uses a low level of electrical current to deliver the medication directly through the skin. The product was developed by Alza, and it is marketed in Europe by Janssen-Cilag and in the United States by Ortho McNeil.

In other news on analgesic patches, Daichi obtained a Japanese approval for the once per day delivery of a patch containing Lonoxin, a commonly used NSAID in Japan. Endo Pharmaceuticals introduced Synera, a patch containing 70 mg of lidocaine and 70 mg of tetracaine. The product was developed by Zars, and it is indicated for various dermatological procedures for children and adults. Synera contains an oxygen-activated heating element that automatically warms the skin upon removal from the package and application to skin.

There are a dozen or more transdermal products in Phase II and III development. One of the most exciting is the development of a rivastigmine (Exelon) patch for the treatment of Alzheimer's disease. Others include an Alzheimer's patch for Aricept from Esai/Nitto, analgesic patch for Bupivacaine from Durect, patch for post-herpetic neuralgia using trans-capsaicin from Neurogesx and a patch for osteoporosis using parathyroid hormone 1-34 fragment from TransPharma. The last patch uses Transpharma's microscopic passageways (ablation) technologies.

PASSIVE DIFFUSION

Transdermal Thermal Polymerization (Massachusetts Institute of Technology) US 7097855

A method of drug delivery is described that involves *in situ* polymerization of an agent using transdermal thermal energy. A mixture of a prepolymer (polymerizable material) and an initiator in a suspension or solution is placed subcutaneously using a syringe or through a small surgical incision. Once the suspension or solution is in the desired place, thermal energy is applied over the site for a sufficient amount of time to

polymerize or crosslink the prepolymer with the help of the initiator, yielding a polymer of exactly the required shape and dimensions in the desired location. The suspension can also contain a bioactive agent, which can be trapped in the polymer at the desired site and gradually released over time following biological degradation of the polymer.

Nitric Oxide Donors Capable of Reducing Toxicity from Drugs (Nicox S.A.) US 7087588

A method of reducing gastrointestinal, renal, or respiratory toxicity by transdermally administering a non-nitroderivative drug simultaneously, successively, or previously with an organic compound containing an $–ONO_2$ group or an inorganic compound containing an –NO group is described. The organic or inorganic compound releases NO (nitric oxide) and activates cGMP synthesis when it is present in an amount sufficient to reduce at least one of the above-mentioned types of toxicities. The combination of the nitroderivatives with a non-nitroderivative drug reduces not only the toxicity of the non-nitroderivative drug but also eliminates the disadvantages related to the nitroderivative's administration. The administration of intraperitoneal cisplatin to patients in the presence of a nitroglycerin patch resulted in a very limited increase in blood creatinine compared with the values obtained from administration of cisplatin alone.

Ophthalmic Adhesive Preparations for Percutaneous Adsorption (Senju Pharmaceutical Co., Ltd) US 7052714

The invention consists of an ophthalmic transdermal patch for treating diseases of the posterior segment of the eye, including the lens, vitreous body, choroid, and retina. The patch contains a drug in a base matrix that can be composed of acrylic adhesive, silicone elastomer, or styrene-isoprene-styrene copolymer and contains percutaneous absorption enhancers such as a mixture of 20% (w/w) of polyoxyethylene oleyl ether and 10–20% (w/w) of isopropyl myristate. This invention presents an advantage for drugs such as anti-cataract agents, anti-inflammatory agents, anti-viral agents, immunosuppressants, calcium channel antagonists, glutamate receptor antagonists, or cysteine protease inhibitors, which hardly reach the posterior segment of the eye by topical instillation or subconjunctival injection.

Ultra Thin Film Transdermal/Dermal or Transmucosal/Mucosal Delivery System (Corium Corporation) US 7049479

A transdermal, dermal, transmucosal, or mucosal active delivery system is provided that utilizes an ultra thin polymeric film (under 0.002 in.) adhered on one side to a first adhesive layer that has a handling member that partially extends beyond one edge of the ultra thin polymeric film. The other side of the ultra thin polymeric film is adhered to a second adhesive layer that has a release liner on its other side. An active ingredient or active ingredient coating compound can be incorporated into the second adhesive layer or is otherwise secured or adhered to the first side of the ultra thin polymeric film. The second adhesive layer adheres more aggressively to skin or mucosa than the first adhesive layer adheres to the second side of the ultra thin polymeric film. Thus, once the first side of the ultra thin polymeric film is adhered to a patient's skin or mucosa, the handling member can be used to remove the first adhesive layer from the ultra thin polymeric film. The ultra thin polymeric film prevents migration of the actives into the backing layer and, thus, decreases the loss of effectiveness of the active ingredient. It also improves the breathability of the film layer and provides flexibility and endurance to the delivery system.

Method and Composition for Rejuvenating Cells, Tissues, Organs, Hair and Nails (Ulrich Peter C et al.) US 7022721

The invention describes unique compounds and pharmaceutical compositions that are capable of uncoupling sugar-mediated coupling of proteins, lipids, nucleic acids, and other biomaterials and any combination thereof. Administration of this composition *in vivo* can reduce deleterious effects, such as the aging process, caused by the sugar-mediated coupling of proteins or other biomaterials. The organism can be exposed to the compound or composition internally by ingestion, transdermal application, or other means. One embodiment of the invention is a topical or dermal application to the skin or eye in the form of a solution, lotion, or ointment and may be formulated with the compound in a suitable vehicle such as water, ethanol, propylene glycol, and a carrier to aid in penetration into the skin or eye.

Patches for external use (Teikoku Seiyaku Co., Ltd.) US 7018647

An external skin patch is described for improved painkilling effect for pains accompanied by inflammation, such as chronic arthrorheumatism, arthrosis deformans, or low back pain. The patch comprises a substrate and a drug reservoir layer coated on the substrate, where the drug reservoir layer contains the drug in an adhesive gel base containing a water-soluble polymeric material, a crosslinking agent, water, and a humectant as essential components. A local anesthetic and a nonsteroidal antiphlogistic analgesic agent can be added as medicinal components. Such patches have excellent drug release controlling function that allows extended transdermal absorption and shows good painkilling effects. An embodiment consisting of a combination of diclofenac sodium and lidocaine showed a 90% amelioration ratio for low back pain in human volunteers, with a remission of 70%.

Transdermally Administered Tolterodine as Anti-muscarinic Agent for the Treatment of Overactive Bladder (Pfizer Health AB) US 7008637

The invention consists of a delivery system containing tolterodine and its salts, prodrugs. and metabolites thereof for transdermal administration in the treatment of overactive bladder. The device can be selected from a group consisting of a reservoir, matrix, drug-in-adhesive, multi-laminate, and polymer-system and can use methods such as iontophoresis, electroporation, electroosmosis, electroincorporation, jet injection, or a combination of the above. The device maintains an hourly flux rate of tolterodine that creates a release profile such

Patent Watch continued on page 30

Patent Watch continued from page 29

that, when applied on the skin at the appropriate time during day or night, a therapeutically effective systemic level of tolterodine prevails, mainly when an effect against overactive bladder is most desirable. One or more transdermal permeation enhancing substance(s) can also be used to increase the amount of tolterodine that may permeate the skin and reach the systemic circulation or to reduce the size of the patch.

Adhesive Mixture for Transdermal Delivery of Highly Plasticizing Drugs (Mylan Technologies, Inc.) US 7070808

A transdermal delivery system that can accommodate highly plasticizing drugs (such as selegiline) is described. The drug can be used in protonated form or deprotonated form in combination with a biocompatible deprotonating agent, where the conversion to the protonated form occurs *in situ*. A specific group of acrylic polymeric adhesives containing between approximately 40% and approximately 90% of a C_4-C_{12} alkyl acrylate as the principal monomeric component have been chosen as the components of the adhesive layer, as they are very compatible with the plasticizing drugs and deprotonating agents. Approximately 10% and approximately 40% (w/w) of a C_1-C_4 alkyl acrylate-hardening monomer can also be added. Embodiments of the patent also include a functionalization monomer or a crosslinking agent that cross links the acrylic polymeric adhesive to form a matrix capable of controlling the release of the drug.

Treatment of Skin Diseases Using a Pharmaceutical Preparation in Colloidal Form (Petrigni Giuseppe) US 7132412

The invention consists of a colloidal mixture of different molecular weight biopolymerized hyaluronic acids, which are naturally occurring biopolymers, and suitable dispersing agents, where the molecular weights of hyaluronic acids used are in the range of approximately 200 to 4,000 kDa, mixed together in different ratios. This colloidal mixture has antiflogistic, antioxidant, and tissue-repair activities that make it particularly effective in the treatment of pathological cutaneous diseases. Though the preferred route of administration is topical, the invention can also be delivered in the form of a transdermal plaster.

Barrier Film Lined Backing Layer Composition and Method for Topical Administration of Active Agents (Noven Pharmaceuticals, Inc.) US 7063859

A flexible transdermal drug delivery system is described where the backing layer of the system is lined, on the side facing the application site, with a liquid-impermeable barrier film, so as to prevent the active agent and/or solvent and/or carrier composition from penetrating into the backing layer. The system has an active agent carrier composition layer with a release liner on one side and the barrier film layer on the other side joined to the backing layer. The barrier film does not interfere with the function of the backing layer and provides sufficient strength and support to anchor the other components of the transdermal system. It allows the system to have flexibility and be able to stretch with movement and at the same time, remain in intimate contact with the application site. Rate controlling membranes can also be incorporated in the system.

Formulations for the Administration of Fluoxetine (Alza Corporation) US 7011844

Compositions, methods, and delivery systems are described for the transdermal delivery of fluoxetine and/or its active metabolites, which have very long plasma half lives. The system can transdermally administer fluoxetine and/or its active metabolites continuously through a body surface at a therapeutically effective rate to achieve and maintain therapeutic blood or plasma levels to treat depression. The skin irritation caused by transdermal administration of fluoxetine is decreased by co-administering it with an anti-irritant corticosteroid, such as hydrocortisone.

Compositions and Methods for Minimizing Adverse Drug Experiences Associated with Oxybutynin Therapy (Watson Laboratories, Inc.) US 7081251, US 7081252, US 7081249, US 7081250

The inventions pertain to the use of a non-oral, slow release composition, such as the transdermal composition of oxybutin, that helps to minimize adverse drug experiences, such as dry mouth, dizziness, blurred vision, and constipation, generally attributed to the presence and amount of active metabolites of oxybutynin, such as, N-desethyloxybutynin. The transdermal composition embodiment of the present invention maintains lower ratios of the mean AUC ratio of the metabolite (N-desethyloxybutynin) to oxybutynin compared with conventional oral dosage forms. The plasma AUC ratio of oxybutynin to an oxybutynin metabolite is maintained in the range of approximately 0.5:1 to approximately 5:1l. Different patch sizes (13–39 cm^2), duration of administration (72–96 hr), and permeation enhancers have been used as variables to maintain plasma concentrations in the above mentioned range. Examples of oxybutynin transdermal administration formulations include 1) topical formulations such as ointments, lotions, gels, pastes, mousses, aerosols, and skin creams; and 2) transdermal patches.

ELECTROMECHANICALLY ENHANCED DELIVERY

Transdermal Delivery Device (Altea Therapeutics) US 7141034 B2

A transdermal delivery device is claimed for forming micropores in a tissue membrane of an animal, comprising a substrate and a porator that is located on or within the substrate, and a controller. The porator is selected from a group consisting of a conducting material, a wire conductor, an adhesive foil, and a screen printed material. The controller applies an electric or thermal stimulus to the porator to initiate pore formation. The substrate is composed of a heat-shrinkable polymer that when exposed to an elevated temperature, due to the activation of the porator, results in a substrate tear that destroys the porator.

Method and Apparatus for Manufacturing a Device (Becton Dickinson) US 7052268 B2

A microbrader can be molded that has microneedles for abrading the stratum corneum to form an abraded site in the tissue for increasing drug delivery. A microdevice can be molded using a mold assembly having a silicon molding surface that can include a recess corresponding to the desired shape and length of the microneedles. The silicon molding surface enables micron- and submicron-size features to be molded from polymeric materials without the polymeric materials adhering to the mold surface. Microneedle sizes claimed are between 5 and 250 μm, and the density of the microneedles is 4–100/mm^2.

Monopolar and Bipolar Current Application for Transdermal Delivery (Transpharma Medical) US 7062317 B2

A device for ablating the skin is claimed for enhancing the delivery of a drug through skin, comprising an electrode applied to the skin, a mechanical sensor that detects the force between the skin and the electrode and generates a sensor signal, and a control unit that receives the sensor signal and directs the electrode to apply a current capable of ablating the skin. The electrode can comprise the drug to be delivered so the current applied to ablate the skin is capable of facilitating delivery of the drug from the electrode through the skin.

Transdermal Delivery and Analyte Extraction (Transpharma Medical) US 7123957 B2

A device for ablating the stratum corneum is disclosed, which includes a plurality of electrodes applied to the subject's skin. A power source applies current between two or more electrodes to ablate the skin, primarily in the area between the electrodes. The ablation facilitates the passage of a drug through the ablated area of the skin during a subsequent time period. The power source can further apply an iontophoretic current to enhance delivery.

Ultrasound Enhancement of Percutaneous Drug Absorption (Light BioScience) US 7004933 B2

A method of enhancing the transport of a drug through the skin entails modifying the skin by removing a follicular plug, skin debris, or part of the stratum corneum, then applying the drug to the skin and exposing the skin to ultrasound. The modification of the skin can be made by mechanical, abrasive, photo acoustic, ablative, thermal, chemical, or enzymatic methods.

Method and Apparatus for Skin Absorption Enhancement and Transdermal Drug Delivery (Mattioli Engineering) US 7010343 B2, US 7083580 B2

A system for enhancing absorption of drugs is provided comprising a probe. The probe comprises an array of electrodes, drug holding unit, and pulse generator configured to generate a sequence of bursts of electrical pulses to the array of electrodes, wherein the pulse generator includes at least first and second transformers arranged to produce out-of-phase pulsing. Optionally the system can include a vibrating unit configured to provide mechanical vibrations to the head of the probe at the same time the electrical bursts are applied.

Compositions for Drug Administration by Electroporation (Pola Chemical) US 7089053 B1

The invention pertains to the increase of drug absorption by electroporation by adding polyhydric alcohols to compositions for electroporation. Compositions claimed consist of essentially the drug, menthol, and 5–30% (w/w) of a polyhydric alcohol. Polyhydric alcohols disclosed include propylene glycol, glycerol, polyethylene glycol, and 1,3-butanediol. Enhancement ratios of over 100 were observed in several experiments.

Device for Transdermal Electrotransport Delivery of Fentanyl and Sufentanil (Alza) US 7018370 B2

A method of obtaining analgesia control is provided, consisting of delivering solely by elecrotransport a dose of 20 to 60 μg of fentanyl within a period of 10–20 min. The delivery can be controlled by the patient and repeated approximately100 additional times per day. The applied electrotransport density is in the range of 50 to 150 μamps/cm^2.

Transdermal Electrotransport Delivery Device Including an Antimicrobial Compatible Reservoir Composition (Alza) US 7054682 B2

A transdermal electrotransport device is claimed comprising an anode, a cathode including an electrode and a reservoir, and an aqueous medium comprising a drug, propylene glycol, and an ionizable antibacterial agent in an amount sufficient to inhibit microbial growth in the aqueous medium. The propylene glycol is present in the range of 5 to 30% to render the ionizable antimicrobial agent compatible with the device. Antimicrobial agents are selected from a group consisting of parabens, chloroxylenol, BHA, propyl gallate, hexetidine, and triclosan and are present in the formulations at the levels of 0.01 to 1% (w/w).

Rate Adjustable Drug Delivery System (Birch Point Medical) US 7016723 B2

A method is claimed of administering rate-adjustable iontophoretic drug delivery by providing power sources and dosage control systems with reliable capacity ratings, the power source, and dosage control systems comprising a plurality of serially connected galvanic couple power sources. The method involves the manufacture of galvanic power sources, determining their capacity characteristics by testing, and serially connecting the galvanic couple power systems into power source and control systems. Labeling can be provided for these systems, indicating average capacity, based on the average charge capacities of corresponding tested lots from which the plurality of galvanic power sources are taken.

Controlled Dosage Drug Delivery (Birch Point Medical) US 7031768 B2

A method is provided for iontophoretically administering a reliable drug dosage by providing a manufactured lot of galvanic battery power sources that include oxidizable species and reducible species and a common conductor for carrying the oxidizable and reducible species. The dosage control is provided by determining by sample testing an average charge capacity for

Patent Watch continued on page 32

Patent Watch continued from page 31

the galvanic battery power sources and labeling a delivery dosage rating for the devices as verified by the average charge capacity of the tested manufactured lot.

Iontophoretic Drug Delivery Device and Reservoir and Method of Making Same (Vyteris) US 7043297 B2

A method of making a reservoir for an iontophoretic device is claimed, comprising application of a viscous water-soluble polymer solution to one side of a reinforcing member, application of the same viscous water-soluble polymer solution to a release liner, lamination of the release liner and the reinforcing member together in such a way that both surfaces of the reinforcing member are coated, and crosslinking of the viscous water-soluble polymer solution by high energy irradiation. The thickness of the crosslinked water-soluble polymer is between 5 and 30 mils. The only drug specifically claimed is lidocaine, which is formulated together with a vasoconstrictor, a stabilizer, and glycerin. ■

Contribute to the CRS Graduate Student Travel Grant Lottery when you register for the Annual Meeting & Exposition. Contributions of $25 or more will be acknowledged in Long Beach. Thank you for your donations to the future of controlled release and delivery.

2007 Controlled Release Society Exposition

Make connections with more than 100 of the leading companies in the industry to find the latest products, technologies, publications, and services for controlled release and delivery while in Long Beach.

3M Drug Delivery Systems
Activaero GmbH
Adhesives Research
Alkermes
Allergan Inc.
Altea Therapeutics
Aptuit Limited
Aqualon, A Business Unit of Hercules Inc.
Asahi Kasei America Inc.
Avanti Polar Lipids Inc.
Azopharma
Banner
BASF Corp.
Baxter Healthcare Corp.
Bilcare Inc.
Bio-Images Research Ltd.
Biovail Contract Research
Boehringer Ingelheim Chemicals Inc.
BRACE GmbH
Brookwood Pharmaceuticals
Buchi
Capsulution NanoScience AG
Cardinal Health
Carpe Diem, A Wiley Company
ChemAgis USA Inc.
ChemImage Corp.
CMA/Microdialysis Inc.
Coating Place Inc.
Colorcon
CyDex Inc.
Degussa
Distek Inc.
DPT Laboratories Ltd.
Dr Reddy's Laboratories Inc.
Drug Delivery Technology
Duoject Medical Systems
DURECT Corporation
Elan Corporation
Elsevier
ERWEKA GmbH
Gaylord Chemical Corp.
Genzyme Pharmaceuticals
Glatt Air Techniques
Halozyme Therapeutics
Hanson Research
Hisamitsu Pharmaceutical Co. Inc.
Hovione
ICON Development Solutions
Inabata America
Informa Healthcare
Innojet Technologies
Inotech Biosystems Intl
IOMED Inc.
Irvine Pharmaceutical Services
ISP
LCI Corporation
Lipoid LLC
LTS Lohmann Therapy Systems
Malvern Instruments
Microfluidics
Molecular Profiles Ltd.
Mylan Technologies Inc.
Northern Lipids Inc.
NovaMatrix & FMC Biopolymer
Noven Pharmaceuticals Inc.
Noveon Inc.
O'Hara Technologies Inc.
OctoPlus
OnDRUGDelivery
Oxford Instruments
Patheon Inc.
Penn Pharmaceutical Services Ltd.
Pharma Circle
Pharma Magazine
Pharma Test Americas
Pharmaceutical Profiles
Pharmaceutical Technology
Phoqus Pharmaceuticals Limited
PII
PolyMicrospheres-Advanced Nanotechnologies
Polymun Scientific GmbH
PURAC Biomaterials
Scintipharma Inc.
SCOLR Pharma Inc.
Shin-Etsu Chemical Co Ltd.
Simulations Plus Inc.
Soliqs
Sotax Corporation
Southwest Research Inst.
SPI Pharma
Surface Measurement Systems Ltd.
SurModics Inc.
Sympatec Inc.
Symyx Technologies Inc.
Technology Catalysts Intl.
TeraView Ltd.
Texture Technologies
Travanti Pharma Inc.
Varian Inc.
Vector Corp.

InTheNews

Compiled by Steven Giannos
Industrial Editor

Bioject Develops Canine Melanoma Device for Merial Ltd.

Health & Medicine Week via NewsEdge Corporation (NewsRx.com): April 9, 2007 – Bioject Medical Technologies Inc. (NASDAQ:BJCT), a leading developer of needle-free drug delivery systems, has announced that it has developed a canine melanoma device for Merial Ltd., a leading animal health company, for use with Merial's canine melanoma vaccine for dogs. The USDA has approved the vaccine, and Merial will be launching it with Bioject's modified Vitajet™3 spring-based device.

Bob Nordgren, head of research, technology acquisition and North American biological development at Merial commented, "In studies conducted at the Animal Medical Center, the combination vaccine and device showed success in prolonging survival time in dogs with oral melanoma. We look forward to providing the animal health market with the vaccine via needle-free delivery." "Once again we have shown an improved delivery system for the delivery of a specific vaccine. We have worked many years with Merial and the Animal Medical Center to improve the treatment and care for animals with melanoma," said Dr. Richard Stout, executive vice president and chief medical officer. "We are pleased to have delivered the melanoma device to Merial for use with the vaccine," said Jerald S. Cobbs, chair, interim president, and CEO of Bioject, "and we continue to look forward to offering Merial other needle-free products. A similar DNA-based vaccine for humans using our Biojector® 2000 device is currently in clinical trials."

Carrington Laboratories and International Vaccine Institute Collaborate on Sublingual Vaccines

Health & Medicine Week via NewsEdge Corporation (NewsRx.com): April 9, 2007 – Carrington Laboratories Inc. (NASDAQ:CARN) announced its wholly owned subsidiary DelSite Biotechnologies, Inc. has entered into a collaborative agreement with the International Vaccine Institute (IVI) to evaluate DelSite's drug delivery technology for sublingual vaccines that can be used for needle-free immunization programs in needy areas of the developing world. IVI is an internationally renowned organization that was established at the initiative of the United Nations Development Program to accelerate development and introduction of new and existing vaccines for poor populations of the developing world and to transfer new technologies to vaccine producers.

The collaborative agreement states "[DelSite's] polymer is capable of gelling *in-situ* in contact with body fluids, including the oral fluid, and is mucoadhesive, which together provide the formulation prolonged residence time and a sustained antigen release. In addition, the polymer has an antigen stabilization effect. The formulation can be prepared in various forms—a liquid, a soft gel, a powder, or a dried pad." Under the collaboration, during the next 12 months, Carrington will formulate vaccine antigens supplied by IVI for sublingual delivery, and IVI will conduct animal testing. The target vaccine antigens and formulation forms will be selected by mutual agreement.

During the term of the agreement, DelSite has agreed to not enter into another agreement to use GelSite®, its polymer delivery technology for sublingual vaccines, without the consent of IVI. Arrangements for commercial development and marketing of vaccine candidates generated by the collaboration would be decided on by Carrington and IVI as equal joint owners of the prospective products.

Dr. Turner, President and CEO of Carrington Laboratories, Inc., added that IVI's interest in the GelSite® technology, as well as other recently announced agreements—with EndoBiologics, Missoula, Montana, for the use of GelSite® in development of a vaccine for bacillary dysentery (shigellosis); AriaVax, Gaithersburg, Maryland, for an HIV vaccine; and ElSohly Labs, Oxford, Mississippi, to use GelSite® formulating an anticancer drug—demonstrates the versatility of DelSite's platform technology for delivering vaccines and therapeutic agents. DelSite's nasal powder vaccine delivery platform is also being evaluated as a delivery system for an H5N1 pandemic influenza vaccine, partially supported by a NIH/NIAID Challenge Grant, and under a CRADA with the NCI, DelSite is investigating its utility for nasal delivery of an HPV vaccine.

Alpharma Licenses Novel Technology from Tris Pharma

NewsRx.com: April 5, 2007 – Alpharma Inc. (NYSE:ALO), a leading global specialty pharmaceutical company, announced it has entered into an exclusive licensing agreement with Tris Pharma, Inc. (Tris), a privately owned specialty pharmaceutical company engaged in the research and development of drug delivery technologies. Under the terms of the agreement, Alpharma will gain access to Tris' LiquiXR™ technology, a novel and proprietary drug delivery platform for sustained release products in liquid form. The company plans to use this technology to develop an oral liquid product complementary to the company's KADIAN® solid-dose product line. This planned addition to the KADIAN® product line is targeted to address the significant unmet need for liquid-dose sustained release opioids, especially in the long-term and institutional care markets.

In addition, Alpharma is collaborating with Tris to leverage its technology to further improve the attributes of the KADIAN® product line. This development program will be complementary to Alpharma's abuse deterrent platform, which utilizes the antagonist naltrexone. Both companies will collaborate on the development of

In the News continued on page 34

In the News continued from page 33

these pain management products, and upon approval, Tris will be responsible for manufacturing, and Alpharma will commercialize the products.

Hi-Tech Pharmacal Receives Tentative Approval for Calcipotriene Topical Solution

Medical Letter on the CDC & FDA via NewsEdge Corporation (NewsRx.com): April 5, 2007 – Hi-Tech Pharmacal Co., Inc. (NASDAQ:HITK) announced that the U.S. Food and Drug Administration (FDA) has granted tentative approval to the company's Abbreviated New Drug Application (ANDA) for Calcipotriene topical solution, 0.005%. Hi-Tech's Calcipotriene topical solution is the generic equivalent of Warner Chilcott's Dovonex® topical solution, 0.005% indicated for the treatment of psoriasis of the scalp, which had sales of $13 million in 2006 based on IMS sales data. Hi-Tech does not plan to market its generic version of Dovonex® topical solution prior to expiration of patent 4,866,048, which is due to expire on December 29, 2007.

Hi-Tech is a specialty pharmaceutical company developing, manufacturing, and marketing branded and generic prescription and OTC products for the general healthcare industry. The company specializes in difficult to manufacture liquid and semi-solid dosage forms and produces a range of sterile ophthalmic, otic, and inhalation products. The company's Health Care Products Division is a leading developer and marketer of branded prescription and OTC products for the diabetes marketplace.

Research Conducted at Lovelace Respiratory Research Institute Provides New Information About Pathology

Drug Week via NewsEdge Corporation (NewsRx.com): April 5, 2007 – According to a study from the United States, "The pulmonary route of drug delivery can provide an excellent alternative to other routes both for local lung disease as well as systemic delivery. The year 2006 marks the 50th year since the invention of metered dose inhalers, yet inhalation is a very much underutilized route of delivery, possibly because inhalation drug development is perceived as being too difficult and expensive." "However with proper knowledge these purported difficulties can be overcome. The process begins with identifying the target tissue and then utilizing technologies such as particle size adjustments through formulation techniques and delivery devices to most efficiently deliver the desired dose. There are a variety of new and existing inhaled excipients available to accomplish this goal. The active molecule can also be modified to increase solubility, decrease immunogenicity, and protect it from unwanted metabolism using PEGylation," wrote C. L. Leach and colleagues, Lovelace Respiratory Research Institute. The researchers concluded "Sustained release of an inhaled drug is also possible using biocompatible matrices such as oligolactic acid."

Leach and colleagues published their study in *Toxicologic Pathology* (Inhalation aspects of therapeutic aerosols).Toxicol Pathol, 2007;35(1)23-26. For more information, contact C. L. Leach, Lovelace Respiratory Research Institute, Albuquerque, NM 87108, USA.

New Findings from Institute of Process Engineering Describe Advances in Drug Delivery

Drug Week via NewsEdge Corporation (NewsRx.com): April 5, 2007 – Investigators publish new data in the report "A Thermosensitive Hydrogel Based on Quaternized Chitosan and Poly(ethylene glycol) for Nasal Drug Delivery System." According to recent research from Beijing, People's Republic of China, "A new thermosensitive hydrogel was designed and prepared by simply mixing N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC) and poly(ethylene glycol) (PEG) with a small amount of alpha-beta-glycerophosphate (alpha-beta-GP). The optimum preparative condition was investigated, and the obtained formulation underwent thermal transition from solution below or at room temperature to non-flowing hydrogel around 37 degrees C in several minutes."

"As a new formulation, its potential use as [a] nasal drug delivery system was studied. It can be dropped or sprayed easily into [the] nasal cavity and spread on the nasal mucosa in solution state. After being administered into [the] nasal cavity, the solution transformed into viscous hydrogel at body temperature, decreasing nasal mucociliary clearance rate and releasing [the] drug slowly. Moreover, quaternized chitosan as an absorption enhancer, has been studied extensively in several reports and proved its non-toxicity, mucoadhesivity and the capacity to open the tight junctions between epithelial cells. In this study, insulin was used as a model drug, was entrapped in the formulation and its release behavior *in vitro* was also investigated. The enhancement of absorption of fluorescein isothiocyanate (FITC)-labeled insulin in rat nasal cavity by this formulation was proved by confocal laser scanning microscopy (CLSM). The cytoxicity and the change of the blood glucose concentration after nasal administration of this hydrogel were also investigated. The hydrogel formulation decreased the blood glucose concentration apparently (40–50% of initial blood glucose concentration) for at least 4–5h after administration, and no apparent cytoxicity was found after application," wrote J. Wu and colleagues, Institute of Process Engineering. The researchers concluded "These results showed that HTCC-PEG-GP formulation can be used as [a] nasal drug delivery system to improve the absorption of hydrophilic macromolecular drugs."

Wu and colleagues published their study in *Biomaterials* (A thermosensitive hydrogel based on quaternized chitosan and poly(ethylene glycol) for nasal drug delivery system. Biomaterials, 2007;28(13)2220-2232. For additional information, contact J. Wu, State Key Laboratory of Biochemical Engineering, Institute of Process Engineering, Chinese Academy of Sciences, Beijing 100080, China.

Research from Freie University Berlin, College of Pharmacy, Provides New Information About Drug Delivery

Drug Week via NewsEdge Corporation (NewsRx.com): April 5, 2007 – New research, "A novel *in situ* forming drug delivery system for controlled parenteral drug delivery," is the subject of a report. "The objective of this study was to investigate the *in vitro* drug (diltiazem hydrochloride and buserelin acetate) release from different *in situ* forming

biodegradable drug delivery systems, namely polymer solutions (*in situ* implants) and *in situ* microparticle (ISM) systems. The drug release from ISM systems [poly(D,L-lactide) (PLA) or poly(D,L-lactide-co-glycolide) (PLGA)-solution dispersed into an external oil phase] was investigated as a function of the type of solvent and polymer, polymer concentration and internal polymer phase: external oil phase ratio and was compared to the drug release from *in situ* implant systems and microparticles prepared by conventional methods (solvent evaporation or film grinding)," scientists writing in the *International Journal of Pharmaceutics* report.

"Upon contact with the release medium, the internal polymer phase of the ISM system solidified and formed microparticles. The initial drug release from ISM systems decreased with increasing polymer concentration and decreasing polymer phase:external oil phase ratio. The type of biocompatible solvent also affected the drug release. It decreased in the rank order DMSO >NMp >2-pyrrolidone. In contrast to the release of the low molecular weight diltiazem hydrochloride, the peptide release (buserelin acetate) was strongly dependent on the polymer degradation/erosion. One advantage of the ISM system when compared to *in situ* implant systems was the significantly reduced burst effect because of the presence of an external oil phase. ISM systems resulted in drug release profiles comparable to the drug release of microparticles prepared by the solvent evaporation method," wrote H. Kranz and colleagues, Freie University Berlin, College of Pharmacy. The researchers concluded "Therefore, the ISM systems are an attractive alternative to existing complicated microencapsulation methods."

Kranz and colleagues published their study in the *International Journal of Pharmaceutics* (A novel *in situ* forming drug delivery system for controlled parenteral drug delivery. Int J Pharm, 2007;332(1-2)107-114. Additional information can be obtained by contacting H. Kranz, College of Pharmacy, Freie Universitat Berlin, Kelchstr 31, 12169 Berlin, Germany.

Apogee Signs Exclusive License with Georgia Tech for Microneedle Technology

Market Wire: April 4, 2007, NORWOOD, Mass. – Apogee Technology, Inc. (AMEX: ATA), an emerging developer of advanced drug delivery systems, reported that it signed an exclusive license agreement with the Georgia Tech Research Corporation. Under this agreement, Apogee obtained exclusive rights to a U.S. patent application and know-how related to the design and manufacturing of microneedle-based drug delivery systems. The company believes the technology, when fully developed, will support the efficient manufacturing of its PyraDerm™ intradermal drug delivery system, as well as increase its utility and potential market applications.

David Meyers, Apogee's chief operating officer, said: "We are very pleased to complete a license agreement for technology developed by Dr. Mark Prausnitz and his team at the Georgia Institute of Technology. Dr. Prausnitz, a recognized leader in the field of drug delivery systems, has published more than 80 research articles and holds 15 issued or pending patents. We believe that when the technology is incorporated, we will be able to increase the drug dose our PyraDerm™ system can deliver and thereby expand the potential market applications. In addition, we believe the technology will facilitate the development of the effective manufacturing process consistent with the stringent requirements of the pharmaceutical industry. This is an important evaluation consideration for a pharmaceutical partner who may be interested in licensing and commercializing our delivery system. The technology has shown significant potential in laboratory tests conducted at Georgia Tech, as well as, *in vivo* studies to evaluate vaccine delivery efficiency in an animal model. During the first half of 2007, we plan to incorporate this technology into our delivery system and initiate our own *in vivo* evaluation studies."

Herbert Stein, Apogee's chair and chief executive officer, said, "By combining Georgia Tech's technologies with our technologies we are well positioned to achieve our goal to develop advanced delivery systems. Upon the successful completion of our planned *in vivo* testing in 2007, we intend to pursue agreements with pharmaceutical companies developing and offering high potency protein/peptide drugs and vaccines. Concurrently we are exploring the development of products for the enhanced delivery of active ingredients for applications that may not require regulatory approval, with the goal of generating nearer term revenues for the Company."

Engineers Building Tooth with Built-in Pump for Drug Delivery

Associated Press WorldStream via NewsEdge Corporation: April 4, 2007 – Researchers in Europe and Israel, funded by the European Union, are working on a tiny drug-dispensing system called IntelliDrug that goes into a person's mouth; the ultimate goal is to get the parts small enough to fit into a replacement tooth placed in the back of the mouth like a molar. The device can release a specific amount of medicine at certain intervals, ensuring that the patient gets the proper dosage at the right time. Patients, on average, follow instructions on taking drugs only half the time, even for people who need them to survive, said Dr. Andy Wolff, an Israeli dentist who initially came up with the concept. Patients often forget or find it too inconvenient to take medicine, especially in the middle of the night. He believes the device will rectify the problem by automating the process.

Wolff's company, Saliwell Ltd., and German microelectronics institute HSG-IMIT are two of 15 organizations involved with the development of the device. The project is funded by a program that promotes cooperation between EU nations and Israel. The organizations include universities, companies, research institutes and hospitals. One notable name is Spanish telephone company Telefonica SA, which is helping with the communications technology side of the development.

By placing the device in the mouth, the drug can be delivered directly into the bloodstream through the lining of the cheek and around the mouth, a surface that is porous enough to absorb the medicine. Saliva, meanwhile, mixes with the drug and carries it to the lining more

In the News continued on page 36

In the News continued from page 35

consistently than just swallowing a pill every few hours. "Why in the mouth? It's very accessible, it's very permeable, not like your skin," Wolff said.

The treatment of diabetes is one area where delivering drugs can be advantageous. People with diabetes must take regular injections of insulin to maintain low blood-glucose levels. Instead of pricking their skin, patients can wear the IntelliDrug device for a little while. The device consists of a stainless-steel housing, a pump, and custom valves to regulate drug flow, a microprocessor, batteries, and a reservoir for the drug pill. It is currently a block the size of two teeth and strapped to the side of teeth so it hugs the inside of the cheek. Developers hope to ultimately turn it into a replacement tooth.

The unit can be removed from the mouth so a technician can refill the drug reservoir, clean the system, and replace the battery if needed. IntelliDrug also has a communication port that allows the user to control the device via remote control; the hope is to eventually link it with a cellular phone or a nearby hospital or care center. "This approach combines dentistry with software, communication and technology," Wolff said.

Ongoing clinical trials, on pigs, have been successful. Dr. Axel Schumacher, who is helping design the pumps, said he hopes to have a prototype ready for human testing by the end of the year. Schumacher works for the research institute HSG-IMIT, which is based in southern Germany. So far, the prototypes can only be worn for a limited period. There are hopes that when the components become small enough, they can become a permanent fixture.

Frost & Sullivan Commends Altea Therapeutics for Extending the Frontiers of Transdermal Drug Delivery

PR Newswire via NewsEdge Corporation (PRNewswire): April 3, 2007, PALO ALTO, Calif. – Frost & Sullivan has presented Atlanta-based Altea Therapeutics with the 2007 Frost & Sullivan Technology Innovation Award in the field of transdermal drug delivery for its development of the PassPort™ system, a new breakthrough technology that enables painless delivery through the skin of drugs that until now were administered only by needle injection, including water-soluble drugs, proteins, nucleic acids, and carbohydrates.

The PassPort™ system has dramatically extended the range of diseases that can be treated using transdermal patches. This novel technology has presented a great opportunity for the company in addressing significant medical needs using a method of drug administration proven to lead to high patient compliance. "The Altea Therapeutics PassPort System redefines the scope of transdermal delivery by enabling a cost-effective, non-invasive, and controllable way to deliver a wide range of drugs via the skin," says Frost & Sullivan Research Analyst Bhuvaneashwar Subramanian. "As the solution that finally delivers on the promise of delivery through the skin, the new PassPort System makes more patient-friendly treatments possible for a number of different conditions."

Composed of a PassPort™ patch and a reusable applicator, the technology itself is surprisingly simple to use. The patient clips the patch onto the applicator, places it against the skin, and presses an activation button. Then, as the patient takes the applicator away from the skin, the transdermal patch is automatically positioned on the skin to allow delivery to commence. The applicator can also be configured to record valuable information about patient dosing, including the date and time when the transdermal patch was applied to the skin. The physician can use this information to verify patient compliance and provide proper disease management. Other value-added attributes include the ability to equip the applicator with dose reminder and dose lockout features to prevent drug overdosing, misuse and even abuse. "With its superior functionality and innovative features, the Passport System can potentially be employed for an extensive array of applications ranging from delivering small water-soluble molecules such as apomorphine hydrochloride to treat Parkinson's disease to proteins such as insulin for diabetes management," says Subramanian. "It can also be used for macromolecules such as parathyroid hormone to treat osteoporosis as well as vaccines for disease prevention."

Each year Frost & Sullivan presents this award to a company that has carried out new research that has resulted in noteworthy innovations. These innovations have or are expected to significantly contribute to the industry in terms of adoption, change, and competitive positioning. This award recognizes the quality and depth of a company's research and development program, as well as the vision and risk-taking that enabled it to undertake such an endeavor.

Turning Over a New Leaf with Cellulose Drug Delivery

in-pharmatechnologist.com: March 28, 2007 – A new cellulose-based drug delivery system could be on the horizon, according to a research team presenting their work this week in the United States. The team, led by Dr. Maren Roman of the College of Natural Resources at Virginia Tech, has been working with cellulose nanocrystals—particles with many properties that make them perfect candidates for development of a new generation of drug delivery systems, according to the researchers.

Roman and her colleagues presented their research at the American Chemical Society meeting in Chicago. "Cellulose has been traditionally used for the reinforcement of polymers," Dr. Roman commented. "Otherwise it had been largely overlooked, only gaining more attention recently after all the hype about nanotechnology. We're the first ones to consider cellulose nanocrystals as a drug delivery vehicle."

Cellulose has been routinely used in medical and pharmaceutical applications for many years (for example in pharmaceutical excipients or cellulose wadding for surgical use) and is a very benign material well tolerated by the body. The nanocrystals are a suitable size to be carriers in drug delivery and have many reactive functional groups on their surface to which drugs or targeting molecules could be attached.

With cellulose also representing a renewable resource, it could prove an attractive option for drug manufacturers. Thus far the research team have been

experimenting with targeting molecules, attaching specific antibodies to the surface of the nanocrystals, which would then be injected into the body. "So far we've been working with antibodies, targeting cells that have become inflamed," Roman explained. "The nanocrystals block the receptors on the cell and prevent that mechanism from happening." This process could have applications in combating the effects of certain diseases involving inflammation of blood vessels, such as diabetes, rheumatoid arthritis or some cancers. It's also hoped that the process could be applied to create a new generation of vaccines.

Dow and Colorcon in Controlled Release Collaboration

in-pharmatechnologist.com: March 27, 2007 – Major chemical manufacturer Dow has struck a deal with long-term partner Colorcon, forming an alliance to offer a unified package for the development and production of drug ingredients and products. According to the deal, Colorcon will be responsible for the global marketing, sales, technical service, and development and distribution of Dow pharmaceutical products for use in oral controlled release applications.

The deal only applies to certain polymers and resins from Dow's range, specifically the company's Methocel hypromellose polymers, premium- or NF-grade Ethocel ethylcellulose polymers, and all Polyox polyethylene oxide resins used in pharmaceutical applications. The emphasis of the agreement is on polymers used in controlled release applications, as it has been marked as a high growth area for the companies' customers. According to a Colorcon spokesperson, the company aims to expand the applications of Methocel, Ethocel, and Polyox and provide improved predictive modeling tools for products covered by the partnership.

The alliance is in effect now, though there is a transition period during which distributors will be able to order Dow excipients from the list that will ultimately be covered through the alliance to fulfill customer requirements. This will last until June for the United States, Canada, and Puerto Rico, and September for Europe, Asia Pacific, and Latin America. Colorcon has been a distributor for the products covered by the alliance for almost three decades, and it is hoped that by now bringing all the products under one roof excess activity at both firms can be reduced and speed-to-market for customer products can be significantly improved. The multi-year agreement will facilitate all stages of a project from choosing and sourcing excipients, initial technology development, and through to final commercialization and product delivery, all through a single project director.

Colorcon will take over projects and customer accounts, as well as supply chain, for most of the existing accounts. Colorcon will now be the sole distributor of all Dow excipient polymers for all pharmaceutical applications in Europe, Asia, and Latin America. In the United States and Canada, Colorcon will become the sole distributor of Ethocel and Polyox for all pharmaceutical applications and the sole supplier of Methocel products in controlled release applications (Methocel products for other applications will remain available through Dow's other distributors). In Japan, the company will assume distributor status for Methocel and Polyox products as of July 2007, and Ethocel will join the portfolio during 2008.

Skyepharma PLC Completes Disposal

Market Wire via NewsEdge Corporation: March 26, 2007: LONDON, UK – SkyePharma PLC (LSE:SKP; NASDAQ: SKYE) has announced that the Paul capital refinancing and the disposal of the injectable business have been completed. As such, the placing of the new ordinary shares is no longer conditional and will raise GBP14.8m (net of costs). This completes the major financial restructuring announced on January 9, 2007.

SkyePharma is now able to focus on organic growth of its business by completing the development of its unique combination product Flutiform™ (fluticasone/formoterol inhalation treatment for asthma), which is in phase III development, as well as seeking additional opportunities to leverage the group's proven range of skills and technologies in developing oral and inhalation products. Frank Condella, SkyePharma's chief executive, said: "The completion of the disposal has removed the cash burn attributable to the Injectable Business and has significantly strengthened the Company's balance sheet and cash flows. With the restructuring phase now successfully completed, we can focus fully on the development of SkyePharma's existing oral and inhalation product pipeline, and seek further new opportunities to exploit our unique capabilities in the rapidly growing drug delivery market."

For further information contact SkyePharma PLC at +44 (0)20 7491 1777; Frank Condella, chief executive officer; Ken Cunningham, chief operating officer; Peter Grant, finance director Buchanan Communications at +44 (0)20 7466 5000; Tim Anderson, Mark Court, and Rebecca Skye, Dietrich Trout Group (US); and Seth Lewis at +1.617.583.1308.

Dabur Pharma Launches Nanoxel

India Business Insight via NewsEdge Corporation: March 17, 2007 – Dabur Pharma Ltd. (DPL) has announced the launch of Nanoxel, a novel drug delivery system (NDDS) for the widely used anti-cancer drug, Paclitaxel. This nanoscale drug delivery system is India's first indigenously developed nanotechnology-based chemotherapy agent. DPL is marketing the drug in addition to manufacturing it at its own facility. The drug is a cremophor-free water-soluble formulation and is indicated as an effective and safe therapy for advanced breast, non–small-cell lung and ovarian carcinoma.

Investigators at University of Mississippi, Department of Pharmaceutics, Release New Data on Drug Delivery

Drug Week via NewsEdge Corporation (NewsRx.com): March 16, 2007 – A report, "Iontophoretic drug delivery across human nail," is newly published in the *Journal of Pharmaceutical Sciences*. In this recent report, researchers in the United States conducted a study: "Topical trans-nail delivery of antifungal drugs is limited by several physicochemical and physiological factors. Use of chemical permeation enhancers has been a common approach for enhancing trans-nail delivery of drugs."

"The potential of physical permeation

In the News continued on page 38

In the News continued from page 37

enhancement techniques has been found to be higher than the potential of chemical permeation enhancers in transdermal delivery of hydrophilic drugs and macromolecular therapeutic agents. However, application of physical permeation enhancement techniques has not been explored for trans-nail drug delivery. In the current work, iontophoresis was applied across human nail *in vitro* to assess its efficiency in enhancing drug delivery. Salicylic acid (SA) was used as test diffusant. The influence of pH, ionic strength, and current density was studied. Obviously, increase in current density increased the trans-nail transport flux. It appears that about 50–100 mM ionic strength is required for optimal conduction of electric current across nail. The flux enhancement factor (iontophoretic flux/passive flux) also increased with increase in pH due to increased ionization of SA," wrote Murthy S. Narasimha and colleagues, University of Mississippi, Department of Pharmaceutics. The researchers concluded "This study demonstrates the efficacy of iontophoresis in enhancing the trans-nail delivery of drugs."

Narasimha and colleagues published their study "Iontophoretic drug delivery across human nail" in the *Journal of Pharmaceutical Sciences*. J Pharm Sci, 2007;96(2)305-311. For additional information, contact S. Narasimha Murthy, The University of Mississippi, Department of Pharmaceutics, Oxford, Mississippi 38677, USA.

Micro-jets for Painless Needle-free Injections

in-pharmatechnologist.com: March 13, 2007 – Novel needle-free injections that don't cause the pain and bruising common with existing needle-free devices have been developed by a team in California. In a bid to confront the under-use of current needle-free methods driven by the pain and discomfort experienced by patients, a team of researchers based at the University of California has developed an alternative, painless, needle-free drug delivery system in collaboration with drug delivery company StratGent Life Sciences.
The new injectors promise to potentially deliver macromolecules, such as vaccines and protein therapeutics, painlessly without the use of a needle, increasing patient comfort and compliance, as well as removing the risk of needle-stick injuries to healthcare workers. Guided by the hypothesis that the cause of the pain and bruising from standard needle-free liquid jet injectors was the result of deep penetration of the jets of the drug into the skin, the team developed a novel injector system that minimizes the depth of penetration using pulsed micro-jets at very high speeds and very small volumes.

"The device consists of a chamber that holds the drug solution," said Dr. Samir Mitragotri, lead author of the research paper on the new technique that was published in the *Proceedings of the National Academy of Sciences*. "The chamber is connected to a nozzle that has a final diameter of about 50-100 micrometers. The chamber is fitted with a piston which is backed up by a piezoelectric crystal, and when a voltage pulse is applied to the crystal it moves forward and pushes the piston. This, in turn, pushes the drug in the form of a small jet which penetrates into the skin."

The pulsed micro-jets are expelled at over 100 m/sec at volumes of just 2–15 nL/pulse. The number of pulses can be varied according to the required drug dose and can be delivered in quick succession to mimic a standard injection or delivered slowly over a period of time in a similar fashion to a conventional transdermal delivery system. The device could also be developed to incorporate multiple nozzles to facilitate higher doses.

Using insulin as a model drug for *in vivo* experiments with rats, the research team was able to demonstrate systemic delivery of macromolecules using their novel micro-jet injector. Although it takes a little longer for the drug treatment to reach the bloodstream using this delivery system compared with conventional injections, the team established bioequivalence of the two methods with absolutely no adverse side effects using the new technique in contrast to the bleeding and bruising observed with traditional jet injectors.

Further research is needed to determine whether any kind of reformulation of current drugs would be required for them to be delivered via this new method, but the ultimate aim of the research group is to establish a technology platform that could be used for the delivery of a variety of vaccines and biotech drugs. "The pulsed micro-jets…open up new possibilities in needle-free delivery of macromolecular drugs," say the researchers. "Compared with hypodermic needles, they offer a needle-free and patient-compliant mode of drug administration. Compared with passive transdermal patches, they allow delivery of macromolecules, provide rapid onset, and controlled, programmable, and precise dosing."

According to the team, the devices could potentially have many applications, including systemic, programmable delivery of drugs (such as insulin for diabetes or fentanyl for pain management), delivery of small doses in superficial layers for use with vaccines, or precise local delivery into the skin which could be used for the treatment of acne or cold sores. Further development is underway to bring the product to a stage where it is ready for the market, and it is too early to accurately estimate the final cost of the novel drug delivery system, said Mitragotri. However, U.S. drug delivery firm StrataGent Life Sciences has been involved with the research to date and is leading commercial development of the new technology.

With around 12 billion needle injections every year for the delivery of vaccines and protein therapeutics such as insulin, growth hormones, and erythropoietin, the novel micro-jet injection devices open up another option in the rapidly expanding needle-free injection market, set to hit US$3billion (€2.3billion) by 2010.

BioLineRx Licenses Novel Drug Delivery System for the Treatment of Solid Tumors and Bone Infections

Business Wire via NewsEdge Corporation (Business Wire): March 12, 2007, JERUSALEM, Israel – BioLineRx Ltd. (TASE:BLRX), Israel's leading drug development company, has announced that it has signed worldwide exclusive license agreements with PolyGene Ltd. and Efrat BioPolymers Ltd. for the development and commercialization of their proprietary polymer drug delivery system designed to improve the efficacy, safety, and ease of administration of a variety of drugs. BioLineRx will continue the development

of the proprietary system for delivering chemotherapy to solid tumors (designated BL-4010) and antibiotics to bone and other infections (designated BL-4011). BioLineRx plans to submit the project for funding by the Israeli Office of the Chief Scientist through BioLine Innovations Jerusalem (BIJ) under the National Biotech Grant received in November 2004.

BL-4010 and BL-4011 are based on a biodegradable polymer, developed by Prof. Abraham Domb, from the Faculty of Medicine, Hebrew University of Jerusalem, and founder and chief scientist of PolyGene and Efrat BioPolymers, that allows the administration of therapeutic agents to the site of the disease while avoiding systemic side effects. The technology is adaptable to a variety of therapies, enhances drug stability, and was shown to be safe in preclinical trials. Unlike currently available drug delivery polymers, the polymer is not water soluble, allowing slow release of the drug from the polymer at a constant rate at the site of injection. Earlier stages of the development of BL-4010 received funding from the Canada-Israel Industrial Research and Development Foundation (CIIRDF).

"We are pleased that BioLineRx has chosen to further develop our novel slow release technology for applications in treating solid tumors and infections," commented Professor Domb. "Our preclinical work has shown promising results including a reduction in tumor size in animal models of multiple types of cancers treated with chemotherapy administered via BL-4010."

Typically, chemotherapy drugs are administered systemically, and it is estimated that only 1% of the drug reaches the tumor site, while causing severe and sometimes treatment-limiting side effects in the rest of the body. The goal of BL-4010 is to minimize drug loss, prevent harmful side effects, and increase the concentration of the drug at the site of the tumor.

The treatment of bone infection involves an aggressive antibiotic treatment for an extended period of time, which can lead to systemic toxicity of the antibiotics. BL-4011 can achieve the necessary high drug concentration at the site of infection while maintaining low systemic drug levels. In contrast to BL-4011, currently available systems developed for local delivery of antibiotics are non-biodegradable and require subsequent removal after the completion of antibiotic release.

Contact: BioLineRx Ltd., Yuri Shoshan (+972.2.548.9100), VP finance and corporate development (yuri@biolinerx.com) or Tsipi Haitovsky (+972.52.598.9892), media liaison (tsipih@biolinerx.com); or Stern Investor Relations, Inc., Melanie Friedman (+212.362.1200 or melanie@sternir.com).

The University of Texas Licenses Drug Delivery Technology to Newly Formed Mimetic Solutions, LLC

Business Wire via NewsEdge Corporation (Business Wire): March 7, 2007, AUSTIN, Tex. – The University of Texas at Austin (UT Austin) announced that it has licensed a drug delivery technology developed by the UT Austin team of Nicholas Peppas, Sc.D., Mark Byrne, Ph. D., and Zach Hilt, Ph.D., to Mimetic Solutions, LLC, an Emergent Technologies Fund IV portfolio company. Dr. Peppas will serve as co-chief scientist of Mimetic Solutions, along with Dr. Hilt, now on faculty at the University of Kentucky. Mimetic Solutions will be managed by Emergent Technologies, Inc. (ETI), with Dr. Brian Windsor serving as managing director.

A pioneer in the field of drug delivery and smart-release systems, Dr. Nicholas Peppas has more than 30 years of research experience and has published more than 1,000 peer-reviewed articles and 30 books. In addition to serving as chief scientist of Mimetic Solutions, Peppas will remain as the Fletcher Stuckey Pratt Chair in Engineering in the Departments of Chemical and Biomedical Engineering and Professor in the College of Pharmacy at the University of Texas at Austin. Mimetic Solutions' core technology, Affinimer™ chemistry, allows for the creation of chemically engineered smart polymers that can bind specific "trigger" molecules, such as a key biomarker in a patient's blood, and subsequently release a drug or other agent under pre-programmed conditions. Managing Director Brian Windsor commented, "Using our proprietary Affinimer™ chemistry we are currently pursuing two major applications: the TheraSmart™ System - smart release of therapeutic agents; and the BeautySmart™ System - smart cosmetic or cosmeceutical delivery." A planned first application is a smart release of insulin in response to blood glucose levels in diabetic patients.

ETI anticipates that the technology licensing deal from the University of Texas at Austin is likely to be one of many to come. In a recent report from the Milken Institute, the University of Texas system was ranked first globally in the number of biotechnology patents filed. "What we do over the next decade in the biotechnology field is crucial," said Neil Iscoe, director of the Office of Technology Commercialization at Austin. "Universities must work closely with entrepreneurs, investors, and established industry to move nascent scientific discoveries into products that will bring significant value to society, addressing issues of health, productivity, and quality of life."

Contact: Mimetic Solutions, LLC Brian Windsor, Ph.D., +1.512.263.3232, ext. 202 or info@mimeticsolutions.com.

Liposome Technology to Help DNAi-Based Cancer Drug Delivery

in-pharmatechnologist.com: March 7, 2007 – Biotech company ProNAi Therapeutics plans to use a new liposome technology to help deliver its new class of DNA interference (DNAi)-based drug. Delivering nucleic acid-based drugs successfully to internal tissues is a tough challenge, and ProNAi has been working with Novosom to develop an effective way to deliver its PNT100 drug candidate using its "Smarticles" technology, which it now plans to license.

"We have developed a GMP-enabling oligo delivery method that allows us to submit an IND, and we expect more significant milestones to be met in the near future," said Richard Gill, president and CEO of ProNAi. "The successful delivery of nucleic acid-based drugs has been the 'holy grail' of the industry for many years, and we are confident that our

In the News continued on page 40

In the News continued from page 39

combined approach will yield promising outcomes."

U.S. firm ProNAi is a biopharmaceutical company currently developing DNAi-based drug candidates with the potential to treat cancers, including non-Hodgkin's lymphoma and breast and colon cancer. Germany's Novosom has developed a formulation technology under the "Smarticles" banner that has been shown to deliver nucleic acid sequences into cells effectively.

Novosom's technology is based on lipid particles (liposomes), a vehicle that has been used for many years to deliver drugs with poor bioavailability. Like conventional liposomes, the firm's Smarticles are stable in blood and distribute in the same manner, but they have one fundamental difference. They become positively charged when they cross cell membranes, leading to effective delivery of their cargo within cells. The liver and spleen, along with sites of inflammation and tumors, are primary targets for the charged liposomes.

First Anti-psychotic Patch in Development

in-pharmatechnologist.com: March 6, 2007 – Two U.S. companies have teamed up to develop a prototype patch to deliver an existing anti-psychotic drug through the skin. If successful, the move would represent a market breakthrough, as there is currently no transdermal version of any anti-psychotic drugs, according to the firms.

Under the terms of the deal, drug delivery company Dermatrends will provide the drug delivery technology for transdermal delivery of an anti-psychotic drug selected by Teikoku Pharma USA. "In terms of clinical compliance, it is better than the oral version," said Lee Schafer, a Dermatrends spokesperson. "You can put the patch on the back of a patient for example where it is difficult to reach and it is easier to monitor that the patient is actually taking the medication." Details about the patch have not been disclosed, but Schafer said it would probably be a once daily administration.
While there is no assurance that the two firms will enter into a joint development or licensing deal as a result, Dermatrends CEO Ted Schwarzrock said he is optimistic about prospects for positive results from the development of this prototype. "We have produced positive efficacy results for many of our products, including similar compounds to the one we are testing for Teikoku," said Schwarzrock. "Our mission is to help demonstrate that Dermatrends' patented hydroxide releasing agent (HRA) technology can be combined with the chosen active pharmaceutical ingredient (API) to produce a proprietary pharmaceutical product for our new partner." He added that his company believed that transdermal delivery could be a preferred method of delivery for many patients and represents an important new market opportunity.

Schafer said that his company expected to make a decision at the end of 2007 when the proof of feasibility is completed and that he hoped Dermatrends and Teikoku could continue working together.

Nitto Denko Subsidiary Develops Novel Drug Delivery Technology Platform; Higher Drug Efficacy with Fewer Side Effects Expected

Comtex Business via NewsEdge Corporation (JCN Newswire): February 13, 2007, OSAKA, Japan – Japan's leading diversified materials company Nitto Denko Corporation has developed, at its wholly owned U.S. R&D subsidiary Nitto Denko Technical Corporation(NDT), a platform technology for a novel drug delivery system (DDS) using a biodegradable polymer material, the company announced, adding that the development has been conducted in collaboration with the University of California, San Diego (UCSD).

Located in Oceanside, California, NDT is engaged in high-tech research in various fields, including biomedical materials. It is a member of Nitto Denko Group, composed of Nitto Denko and its 117 subsidiaries in 24 countries around the world. The technology NDT developed together with the Moores Cancer Center of UCSD takes advantage of a biodegradable and biocompatible polymer material that, when linked to certain therapeutic agents, can greatly enhance the drug's solubility and act as a "carrier," with promising potential to deliver such agents to the target tissue with high efficiency.

While not possessing any therapeutic properties per se, the polymer-based carrier has shown the potential to increase therapeutic efficacy and offer the benefit of reduced side effects when conjugated to existing drugs. In addition, it has the potential to serve as a carrier for a large number of compounds in a range of therapeutic classes, for treating a wide variety of diseases.

Nitto Denko possesses a strong portfolio of transdermal drug delivery technology, including asthma patches and patches for ischemic heart disease, with a large share in the Japanese market. Having added to its Medical Division a U.S. company Aveva Drug Delivery Systems (www.avevadds.com) in Florida in 2003, Nitto Denko Group is actively engaged in further expanding the business of manufacturing and selling transdermal drug delivery patches.

The technology developed by NDT is consistent with Nitto Denko's plan to increase its profit margins by leveraging its expertise in polymer synthesis to increase its business in the lucrative drug delivery industry. Aside from this new technology, NDT has also been engaged in extensive research into biomedical material applications by leveraging Nitto Denko's polymer synthesis capabilities to develop a gene delivery reagent based on a biodegradable cationic polymer, as well as a polymeric solid support for oligonucleotide synthesis and biomedical-related technologies.

Contact: Kazuhito Kouno Corporate Communications, Corporate Brand Management Department Nitto Denko Corporation at Tel: +81.6.6452.2215 or Fax: +81.6.6452.3316.

Pump Technology Sustains Insulin Patch

in-pharmatechnologist.com: February 6, 2007 – U.S.-based start-up company Medipacs is developing a miniaturized digital pump, no bigger than a quarter, which could become the first patch-like product to help diabetics manage their

insulin therapy. Medipacs has been in talks with companies to produce a patch able to hold a 72-hr insulin dose, while pumping out 1 mL over 24 hr, which will match the shelf life of insulin. The patch is a scaled-down version of a larger pump, also in development, which would be used for delivering active drugs over a 2-week period. Another feature is that the patch is flexible enough to be programmed with a patient's required delivery rate. The firm expects the patch to hit the $2 billion drug delivery patch market in 24–30 months.

Medipacs' patch is attached to the skin by adhesive and is used with skin barrier technologies, such as micro needles, phonophoresis (ultrasound), and electrophoresis (applied electric field). The firm explains that the pump runs on a small amount of power, less than 3 V. The system's backpressure is more than enough to deliver insulin, which would require 5 psi but can operate at a higher psi so it can be used for liquid pharmaceuticals with a higher viscosity.

The pump is still in research and development but the technology has been proven to operate over 72 hr and can sustain backpressure of 30 psi. The company hopes that a larger pump will become a commercial reality within 18–24 months, where it would enter an infusion pump market worth US$2 billion (€1.54 billion).

"Ultimately we want the pump to be able to run continuously for extended lengths of time as long as two weeks to a month so it can be used in the larger form of a portable infusion pump. The Medipacs technology will have a dramatic impact on lowering the cost of healthcare for patients that need delivery of liquid drugs and fluids over extended times," said Sonia Vohnout, Medipacs systems engineer. "We have proven the concept and are now working on medical applications for the first commercialized products, once we have funding to proceed we are 18-24 months from market introduction," said Mark Banister, president of Medipacs.

IGI and Novavax Enter into License Agreement

Vaccine Weekly via NewsEdge Corporation (NewsRx.com): February 01, 2007 – IGI, Inc. (IG) announced that Novavax, Inc. and IGI have entered into an agreement that would expand Novavax's existing strategic alliance with Bharat Biotech International, Ltd., of India.

Under the agreement, Bharat will have rights to develop certain vaccines for animals using Novasomes for India and other selected markets. IGI is licensing back to Novavax a nonexclusive license with the right to sublicense to Bharat rights related to the use of Novasomes as adjuvants for animal vaccines. Bharat will fund all preclinical and clinical development. IGI and Novavax will share royalties on products developed using Novasome encapsulated delivery technology to treat diseases in animals and vaccines developed to combat the avian flu virus in birds. "IGI believes this agreement could result in other opportunities between IGI and Novavax," said IGI Chairman Frank Gerardi.

IGI is a company committed to growth by applying proprietary technologies to achieve cost-effective solutions for varied customer needs. IGI offers the patented Novasome lipid vesicle encapsulation technology, which the company says contributes value-added qualities to cosmetics, skincare products, dermatological formulations, and other consumer products, providing improved dermal absorption, low potential for irritations, controlled and sustained release, as well as improved stability. IGI has exclusive rights for the Novasome adjuvant technologies for animal vaccines.

Ranbaxy Unveils Two Urology Products Based on Novel Drug Delivery System

India Business Insight via NewsEdge Corporation: February 1, 2007 – Ranbaxy Laboratories Ltd. (RLL) has launched two novel drug delivery system (NDDS) urology products in the Indian market.

It has developed the first product, Niftran 100-mg capsules, using its research and development capabilities. The second product launched by RLL, Eligard 22.5-mg and 45-mg, has been in-licensed from QLT Inc. of the United States. Niftran offers a 2-times-a-day dosage compared with the 4-times-a-day dosage with the existing Nitrofurantoin, while Eligard is an NDDS-based hormonal therapy product used in the treatment of advanced prostate cancer.

Investigators at Cardiff University, Center for Polymer Therapeutics, Publish New Data on Drug Delivery

Drug Week via NewsEdge Corporation (NewsRx.com): February 1, 2007 – Scientists discuss in "Thermo- and pH-responsive polymers in drug delivery" new findings in drug delivery. According to recent research from Wales, "Stimuli-responsive polymers show a sharp change in properties upon a small or modest change in environmental condition, e.g. temperature, light, salt concentration or pH. This behaviour can be utilised for the preparation of so-called 'smart' drug delivery systems, which mimic biological response behaviour to a certain extent."

"The possible environmental conditions to use for this purpose are limited due to the biomedical setting of drug delivery as [an] application. Different organs, tissues and cellular compartments may have large differences in pH, which makes the pH a suitable stimulus. Therefore the majority of examples, discussed in this paper, deal with [a] pH-responsive drug delivery system. Thermo-responsive polymer is also covered to a large extent, as well as double-responsive system. The physico-chemical behaviour underlying the phase transition will be discussed in brief," writes D. Schmaljohann and colleagues, Cardiff University, Center for Polymer Therapeutics. "Selected examples of applications are described."

Schmaljohann and colleagues published their study in *Advanced Drug Delivery Reviews* (Thermo- and pH-responsive polymers in drug delivery. Adv Drug Deliv. Rev, 2006;58(15)1655-1670. For additional information, contact D. Schmaljohann, Centre for Polymer Therapeutics, Welsh School of Pharmacy, Cardiff University and Cardiff Institute of Tissue Engineering and Repair (CITER), Redwood Building, King Edward VII Avenue, Cardiff, CF10 3XF, Wales, UK.

In the News continued on page 42

In the News continued from page 41

Smokable Pain Drugs Promise Faster Action

Turkish Daily News via NewsEdge Corporation: February 1, 2007 – All self-respecting painkillers these days offer "fast-acting relief," a promise we accept to mean anywhere from 15 minutes to more than an hour. For Alexza Pharmaceuticals Inc., which is developing drugs for migraine, pain, panic, and agitation, "fast" has to mean "within seconds." The Palo Alto, California-based company is developing drugs that can be "smoked," and, like nicotine in cigarettes, pass through the lungs and into the bloodstream almost instantly.

Alexza was formed by biotechnology entrepreneur Alejandro Zaffaroni, who also founded nicotine patch developer Alza. His latest venture is not the only company that is developing inhaled therapies: Nektar Therapeutics and Alkermes Inc. are developing powdered insulin. But, Alexza's idea of heating up a drug to create a vapor, or smoke, is unique.

The company's lead product is a vaporized version of an old drug called prochlorperazine, which Alexza is developing for migraine headaches but is currently used in liquid, oral or suppository form to treat severe nausea. While it is sometimes given intravenously in hospitals to treat patients with acute migraines, the drug is inconvenient to deliver. Alexza is hoping to provide similar results but in such a way that patients can carry the delivery device -- an inhaler that looks like a miniature hip flask -- in a pocketbook or the glove compartment of a car. The device contains a battery-powered package that heats a thin coating of drug to create a vapor that can be sucked into the lungs.

The company planned to release initial results of a mid-stage clinical trial of its migraine drug by the end of March. If all goes according to plan, Alexza could file a marketing application with U.S. regulators in 2010. The company is also testing inhalable drugs for pain and anxiety and for agitation in schizophrenia patients.

Reports Summarize Post-operative Pain Therapy Research from University of Edinburgh

Pain & Central Nervous System Week via NewsEdge Corporation (NewsRx.com): February 1, 2007 – According to recent research published in the journal BJA, "The fentanyl HCl iontophoretic transdermal system (fentanyl ITS) is a novel patient-controlled analgesia (PCA) system that has been approved in the USA and Europe for the management of acute, moderate-to-severe postoperative pain. This system extends the applicability of transdermal drug delivery to acute pain management, allowing patients to self-administer pre-programmed doses of fentanyl non-invasively through the use of iontophoretic technology."

"Iontophoresis is the process by which an electric current is used to drive ionized drug molecules across the skin and into the systemic circulation. Results of a recent US clinical trial found the fentanyl ITS to provide pain control equivalent to a standard regimen of morphine i.v. PCA, with a similar incidence of opioid-related adverse events. The fentanyl ITS may offer a number of clinical advantages over existing PCA modalities. Its method of drug delivery avoids the risk of complications from needle-related injuries and infection, and its pre-programmed electronics eliminate the potential for manual programming errors and excessive dosing. In addition, the compact size of the system could enable greater patient mobility following surgery," wrote I. Power and colleagues, University of Edinburgh. The researchers concluded "The fentanyl ITS has the potential to become a valuable option in the management of acute postoperative pain."

Power and colleagues published their study in BJA (Fentanyl HCl iontophoretic transdermal system (ITS): Clinical application of iontophoretic technology in the management of acute postoperative pain. BJA 2007;98(1)4-11. For additional information, contact I. Power, The University of Edinburgh, Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary Little France, Edinburgh EH16 4SA, UK.

Patching up Alzheimer's Safely

in-pharmatechnologist.com: January 24, 2007 – US-based researchers have developed a transdermal vaccine for Alzheimer's disease that has been shown to clear brain-damaging amyloid plaques in preclinical studies, offering hope to millions of sufferers worldwide.

Researchers at the University of South Florida (USF) suggest that the patch-based delivery approach will not be associated with toxicities that have caused problems with other injectable vaccines for Alzheimer's. The group claims it is the first to show that a transdermal vaccine, which triggers the immune system to clear amyloid beta—a protein found in abnormal quantities in the brains of Alzheimer's patients—can be effective and safe. "Specialised immune cells prevalent in the skin, called Langerhans cells, may direct the body's reaction to the vaccine toward a response that is beneficial instead of overly aggressive and ultimately harmful," said Jun Tan, USF.

A number of AD vaccines have been developed in the past few years, but they are still in development, with acetylcholinesterase inhibitors (AchI) currently dominating the market despite limited efficacy. The global Alzheimer's disease therapeutics market is predicted to grow 11% each year, reaching US$3.05 billion in 2009.

A vaccine for Alzheimer's disease developed by Elan and Wyeth that used modified beta amyloid as an antigen entered clinical trials in 2002, but testing had to be stopped abruptly after some patients developed brain inflammation. The two companies pressed on and in 2005 started an 18-month Phase II trial of another Alzheimer's drug candidate—a monoclonal antibody-based immunotherapeutic called bapineuzumab. Meanwhile, ID Biomedical, recently acquired by UK-headquartered GlaxoSmithKline, has been developing a vaccine for Alzheimer's that combines its novel adjuvant Protollin with glatiramer acetate, the active ingredient in Teva's multiple sclerosis drug Copaxone. And, researchers at Tokyo Metropolitan University recently suggested that DNA vaccines could provide a cheap and effective strategy for treating Alzheimer's in future. Their findings support the idea

that a vaccine is the best hope for fighting this disease for which there is currently no cure.

The global Alzheimer's drug market has been dominated by Pfizer's Aricept (donepezil), which holds over 50% of the global market. Novartis' Exelon (rivastigmine), Ortho-McNeil's Razadyne/Reminyl (galantamine), and Forest Laboratories' Namenda (memantine) share the remainder. Future USF research plans include testing whether the transdermal vaccine also affects the memory loss often associated with Alzheimer's patients. The researchers have described their results in a recent article in *Proceedings of the National Academy of Sciences*. ■

CRS Annual Meeting & Exposition Closing Reception/Banquet

Tuesday, July 10

You'll want to join your colleagues for this festive evening at the Aquarium of the Pacific. The Aquarium of the Pacific is home to 12,500 marine animal species from three Pacific Rim regions: Southern California/Baja, the North Pacific and the Tropical Pacific. Enjoy your favorite beverage as you view the more than 12,000 ocean animals on display in exhibits ranging in size from 5,000 to 350,000 gallons! After the reception, a banquet dinner will be served followed by award presentations. Seating is limited, so register early!

See #10 on the registration form (ticket price includes Aquarium admission).

Journal of Controlled Release *Highlights*

By Kinam Park

Three New Initiatives at JCR

The *Journal of Controlled Release* (JCR) provides a forum where drug delivery scientists present new findings and communicate interesting results. In each issue, papers are grouped, and similar topics are presented together for easy identification. JCR also publishes review articles on selected topics. Another important section of JCR is the Gene Delivery section, which continues to enjoy success in terms of the number of papers published and its impact on the field. To better serve its readers, JCR plans to add two new initiatives: Perspective and Nanotechnology sections.

Perspective Section

The Perspective section presents a personal view on the future of a selected topic and not the collection of information from the past. A Perspective is different from regular research articles in that the view presented may not be based on the data, but on a personal belief on how future research may evolve and the impact it may have on the field, as well as society. The first Perspective will be on the topic of nanotechnology, specifically focused on how nanotechnology can benefit the field of drug delivery. Subsequent Perspectives will deal with important topics facing the research community today, including molecular imaging and drug delivery, drug-eluting stents, biomedical device-drug combination products, viral versus non-viral gene delivery, and the paradigm shift in transdermal drug delivery.

Nanotechnology Section

The second new initiative is a new section on Nanotechnology. This is an extension of the highly successful Gene Delivery section. JCR has seen a notable increase in manuscripts received based on nanotechnology. As a result, a new section will be dedicated to new drug delivery systems based on nano/micro fabrication. This new section will serve as a forum focused on new delivery systems designed using non-traditional methods.

I encourage all members of the Controlled Release Society to suggest potential topics and authors for the Perspective section, as well as other already established sections, of the JCR. JCR has been enjoying fast growth because of its dedicated members, and I believe that with your support the two new initiatives will make JCR even more successful. I look forward to receiving your valuable suggestions and contributions. ■

Top Downloaded Papers from the *Journal of Controlled Release*

Below is a list of the 25 top downloaded papers in the JCR for the last quarter.

Polyionic hydrocolloids for the intestinal delivery of protein drugs: Alginate and chitosan – A review • Review article. George, M., and Abraham, T.E.
Journal of Controlled Release, 114(1):1-14, 2006

Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective • Review article. Ratnam, D.V., Ankola, D.D., Bhardwaj, V., Sahana, D.K., and Kumar, M.N.V.R.
Journal of Controlled Release, 113(3):189-207, 2006

Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach • Review article. des Rieux, A., Fievez, V., Garinot, M., Schneider, Y.J., and Preat, V.
Journal of Controlled Release, 116(1):1-27, 2006

Development and characterisation of chitosan nanoparticles for siRNA delivery • Article. Katas, H., and Alpar, H.O.
Journal of Controlled Release, 115(2):216-225, 2006

Buccal bioadhesive drug delivery – A promising option for orally less efficient drugs • Review article. Sudhakar, Y., Kuotsu, K., and Bandyopadhyay, A.K.
Journal of Controlled Release, 114(1):15-40, 2006

N-acetyl histidine-conjugated glycol chitosan self-assembled nanoparticles for intracytoplasmic delivery of drugs: Endocytosis, exocytosis and drug release • Article. Park, J.S., Han, T.H., Lee, K.Y., Han, S.S., Hwang, J.J., Moon, D.H., Kim, S.Y., Cho, Y.W.
Journal of Controlled Release, 115(1):37-45, 2006

Molecular design of biodegradable polymeric micelles for temperature-responsive drug release • Article. Nakayama, M., Okano, T., Miyazaki, T., Kohori, F., Sakai, K., and Yokoyama, M.
Journal of Controlled Release, 115(1):46-56, 2006

A dual-ligand approach for enhancing targeting selectivity of therapeutic nanocarriers • Article. Saul, J.M., Annapragada, A.V., and Bellamkonda, R.V.
Journal of Controlled Release, 114(3):277-287, 2006

Biodegradable polymeric nanoparticles as drug delivery devices • Review article. Soppimath, K.S., Aminabhavi, T.M., Kulkarni, A.R., and Rudzinski, W.E.
Journal of Controlled Release, 70(1-2):1-20, 2001

Recent advances on chitosan-based micro- and nanoparticles in drug delivery • Review article. Agnihotri, S.A., Mallikarjuna, N. N., and Aminabhavi, T.M.
Journal of Controlled Release, 100(1):5-28, 2004

Biodegradable nanoparticles loaded with insulin-phospholipid complex for oral delivery: Preparation, *in vitro* characterization and *in vivo* evaluation • Article. Cui, F., Shi, K., Zhang, L., Tao, A., and Kawashima, Y.
Journal of Controlled Release, 114(2):242-250, 2006

Toxicity of cationic lipids and cationic polymers in gene delivery • Review article. Lv, H., Zhang, S., Wang, B., Cui, S., and Yan, J.
Journal of Controlled Release, 114(1):100-109, 2006

Floating hot-melt extruded tablets for gastroretentive controlled drug release system • Article. Fukuda, M., Peppas, N.A., and McGinity, J.W.
Journal of Controlled Release, 115(2):121-129, 2006

Myocardial regeneration strategies using human embryonic stem cell-derived cardiomyocytes • Article. Capi, O., and Gepstein, L.
Journal of Controlled Release, 116(2):211-218, 2006

Block copolymer micelles: Preparation, characterization and application in drug delivery • Article. Gaucher, G., Dufresne, M.H., Sant, V.P., Kang, N., Maysinger, D., and Leroux, J.C.
Journal of Controlled Release, 109(1-3):169-188, 2005

Encapsulated ultrasound microbubbles: Therapeutic application in drug/gene delivery • Review article. Liu, Y., Miyoshi, H., and Nakamura, M.
Journal of Controlled Release, 114(1):89-99, 2006

Transmucosal macromolecular drug delivery • Article. Prego, C., Garcia, M., Torres, D., and Alonso, M.J.
Journal of Controlled Release, 101(1-3):151-162, 2005

Targeted nanoparticles for drug delivery through the blood-brain barrier for Alzheimer's disease • Article. Roney, C., Kulkarni, P., Arora, V., Antich, P., Bonte, F., Wu, A., Mallikarjuana, N.N., Manohar, S., Liang, H.F., Kulkarni, A.R., Sung, H.W., Sairam, M., and Aminabhavi, T.M.
Journal of Controlled Release, 108(2-3):193-214, 2005

Pulmonary delivery of insulin by liposomal carriers • Article. Huang, Y.Y., and Wang, C.H.
Journal of Controlled Release, 113(1):9-14, 2006

PEG conjugated VEGF siRNA for anti-angiogenic gene therapy • Article. Kim, S.H., Jeong, J.H., Lee, S.H., Kim, S.W., and Park, T.G.
Journal of Controlled Release, 116(2):123-129, 2006

Spleen plays an important role in the induction of accelerated blood clearance of PEGylated liposomes • Article. Ishida, T., Ichihara, M., Wang, X., and Kiwada, H.
Journal of Controlled Release, 115(3):243-250, 2006

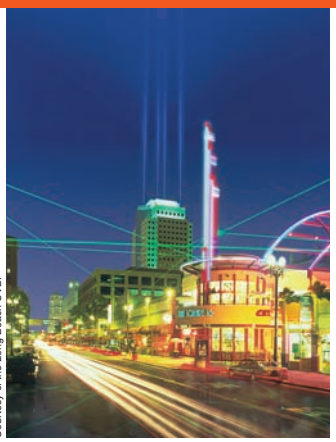
Template synthesis of multifunctional nanotubes for controlled release • Article. Son, S.J., Bai, X., Nan, A., Ghandehari, H., and Lee, S.B.
Journal of Controlled Release, 114(2):143-152, 2006

Microencapsulation by solvent extraction/evaporation: Reviewing the state of the art of microsphere preparation process technology • Review article. Freitas, S., Merkle, H.P., and Gander, B.
Journal of Controlled Release, 102(2):313-332, 2005

Stability of poly(D,L-lactide-co-glycolide) and leuprolide acetate in *in-situ* forming drug delivery systems • Article. Dong, W. Y., Korber, M., Lopez Esguerra, V., and Bodmeier, R.
Journal of Controlled Release, 115(2):158-167, 2006

Polymer micelles with cross-linked ionic cores for delivery of anticancer drugs • Article. Bontha, S., Kabanov, A.V., and Bronich, T.K.
Journal of Controlled Release, 114(2):163-174, 2006 ■

Views of Long Beach



Courtesy of the Long Beach CVB.

Long Beach is California's 5th largest city. With its relaxed atmosphere, scenic downtown, waterfront marina, and five miles of sandy beaches, it's no wonder Long Beach has set the standard as one of America's great walking cities. You'll have plenty of opportunity to soak up those famous California rays with average daytime temperatures of 74-80˚F (23˚C) and an average of 345 days of sunshine annually.

While in Long Beach you will enjoy over 100 restaurants within an eight-block area of CRS' convention hotels and the Long Beach Convention Center. From Pacific Rim to Italian, Mexican to Continental and great seafood, you'll find them all along the wonderful walkway of Pine Avenue in downtown Long Beach. By night, the street is literally ablaze with lights and fun-seeking crowds. There's also plenty of lively and distinctive shopping on Pine and its side streets amidst music venues offering jazz, blues and good ol' rock and roll. The East Village Arts District features one-of-a-kind art galleries and eclectic shops that will amuse and amaze you.

Getting Around Long Beach

Not interested in walking? Catch the convenient Passport shuttle, which runs approximately every 5-10 minutes. It's free in the downtown area and transports visitors to all of the must-see Long Beach attractions, including the Queen Mary, Aquarium of the Pacific, Shoreline Village, and Pine Avenue.

Long Beach is also home to two different water-taxis, each combining a short-harbor cruise with state-of-the-art transportation. The Aquabus is available as your link between selected sites in Rainbow Harbor. Or, hop aboard the new Aqualink catamaran for a swift journey to Alamitos Bay.

For the Art Llovers

The Long Beach Museum of Art's collection is comprised of some 5,000 paintings and drawings with particular strengths in the areas of early 20th century European art and California Modernism. At the western end of Bluff Park, the museum is anchored by a fine craftsman-style home.

The Museum of Latin American Art is the only museum in the western United States dedicated to the work of contemporary Latin artists. The permanent collection spans Latin society from the cultural to the fantastical. Traveling exhibits from Mexico, Central and South America, and the Caribbean are frequent highlights.

Ocean Life

The Queen Mary, once the grand dame of ocean liners, is now a museum as well as a floating hotel with multiple restaurants. Did you know that the Queen was even more luxurious and larger than the Titanic? Celebrities and royalty alike boarded this most glamorous of vessels on its Atlantic crossings from 1934 to 1964.

Pre- and Post-meeting Visitor Options

Catalina Island and Avalon. Let Catalina Express whisk you away to an island paradise in just about an hour. The island remains almost entirely undeveloped and still is primarily a protected nature preserve with a unique ecosystem. The scenic waterfront is lined with great restaurants, perfect for a midday snack or a sunset dinner before heading back to Long Beach.

Universal Studios Hollywood. Universal Studios Hollywood contains within its 415 acres the world's largest movie and television studio, the theme park, and the great shops and restaurants that make up Universal City Walk.

Disneyland and Disney's California Adventure. A short drive south of Long Beach, Disneyland is really a collection of 'lands,' each with its own set of fantastic realities. Right next door, the new Disney's California Adventure celebrates the major wonders—natural and human-made—of the state.

Please visit the CRS website for more information on Long Beach and its attractions and nearby points of interest.

NEWSLETTER
CONTROLLED RELEASE SOCIETY
3340 Pilot Knob Road
St. Paul, MN 55121 USA

calendar of events

who…what…where…when

AAPS National Biotechnology Conference
June 24-27, 2007
San Diego Convention Center
San Diego, California, USA
www.aapspharmaceutica.com/nationalbiotech

34th Annual Meeting of the Controlled Release Society
July 7-11, 2007
Long Beach Convention Center
Long Beach, California, USA
www.controlledreleasesociety.org
ph: 651-454-7250

36th Annual Meeting of the American College of Clinical Pharmacology
September 9-11, 2007
The Palace Hotel
San Francisco, California, USA
www.ACCP1.org

RDPA 2007
September 23-26, 2007
Hotel Hermitage
Biodola Bay, Island of Elba, Italy
www.rdpa2007.com

NanoDDS '07 – Nanomedicine and Drug Delivery Symposium
November 2-3, 2007
Northeastern University
Boston, Massachusetts, USA
www.nanodds.org

AAPS Annual Meeting & Exposition
November 11-15, 2007
San Diego Convention Center
San Diego, California, USA
www.aapspharmaceutica.com/meetings/index.asp

FIP Quality – International 2007 Conference
November 26-27, 2007
Royal Pharmaceutical Society
London, UK
www.rpsgb.org.uk/science

35th Annual Meeting of the Controlled Release Society
July 12-16, 2008
Hilton New York
New York City, New York, USA
www.controlledreleasesociety.org
ph: 651-454-7250