CONTROLLED RELEASE SOCIETY

Volume 24•Number 3•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 3 • 2007

inthisissue

On the cover –

Snapshots of the 34th Annual Meeting & Exposition of the Controlled Release Society in Long Beach, California.

FROM THE Editors

By Yvonne Perrie
Aston University, U.K.

Yvonne Perrie

Dear Reader,

Whilst sitting in front of my blank computer screen, wishfully hoping that my thoughts would turn to something inspiring and interesting, as apposed to dwelling on my new incomprehensible teaching timetable, it occurred to me that I actually had no idea how to write an editorial. Now, I am sure this probably has been blatantly obvious to those who have read one of my previous editorials; however to me it came as a slightly worrying realisation. So, like any highly trained professional I googled "How to write an editorial," and quickly I was enlightened. Of the sites I visited, which was many due to my underlying procrastination, "How to do things.com" offered good guidance. It also rates the difficulty of the task described on a scale of 1–5. Here are a few examples:

1. Writing an editorial – difficulty rating of 3/5
2. Getting a Ph.D. – difficulty rating of 4/5
3. Becoming a college professor – difficulty rating of 5/5
4. How to keep yourself motivated – difficulty rating of 3/5
5. How to improve your communication skills – difficulty rating of 4/5
6. How to clean a cat – difficulty rating of 3/5

So, basically it looks like writing an editorial is as easy as cleaning a cat; should I be reassured by this thought or not I ask myself? Further, from this website it also became clear that there are so, so many things I just don't know how to do. Admittedly about 99% of these things I am sure I will never need to know; however, thinking about it, so much of our day-to-day jobs involve things we are never trained for, such as editorial writing (I add in my defence).

In the web article on how to become a college professor, it advised that a Ph.D. is required. Sound advice indeed, but it does not really offer a solution to my current predicament. Irritated, I mutter to myself that I am an academic, I have a Ph.D., yet no one ever taught me to write an editorial, bla, bla, bla. Therefore, for those who are similarly editorially challenged, here is what I am supposed to do in an editorial:

- Pick an issue, problem, or question
- Pose one or more possible answers
- Weight the evidence supporting possible answers
- Assess counterevidence
- Conclude with an answer

However, now thinking about this, surely this is what we do in our research? So, actually I should be able to do this. Oh well, I know for next time.

Best wishes,

Yvonne ■

CONGRATULATIONS

The CRS would like to congratulate Dr. Robert Langer on the receipt of his National Science Award, which recognises his outstanding contributions to knowledge in the physical, biological, mathematical, or engineering sciences. An interview with Dr. Langer will be published in the next issue of the CRS Newsletter.

CRS Career Connections

Assisting Job Seekers and Employers Achieve Their Goals.

Job Seekers

Post your resume
Search for open positions in YOUR field
Connect with potential employers

Employers

Post open positions
Search and review resumes
Connect with candidates

Take Control of Your Future
Start Your Search Here

www.controlledreleasesociety.org

Susan Cady
CRS President

From the President

By Susan Cady
Intervet Inc., Yardley, PA, U.S.A.

The meeting in Long Beach gave me the opportunity to talk with some of you about the past, present, and future of our society and to listen to what you had to say about it.

The CRS Annual Meeting is a symbol of so much that we do—the science, our interaction with colleagues, and a global forum to exchange ideas and information. As usual, a great CRS Annual Meeting scientific program was presented thanks to the outstanding work by past Scientific Secretary Martyn Davies and the program chairs who made it possible. The venue and organization of events encouraged networking with colleagues and catching up with old friends. Thanks are due as well to our staff. I also thank those of you who completed the attendee survey for the meeting; your input is valuable in making plans for future meetings.

In the next year we will both celebrate our history and look forward to the future, exploring ways to improve and strengthen CRS. The 2008 Annual Meeting in New York City marks our 35th anniversary as a society. We hope to gather the relevant, historical, and unique aspects of CRS to commemorate this anniversary. If you have ideas for celebrating this occasion or are interested in volunteering your time, please contact me or CRS headquarters. Collecting images and stories from the past is an important aspect of the festivities. If you have pictures or anecdotal facts or stories that you would like to share, we invite you to e-mail them to Ronda Thompson at CRS headquarters (rthompson@scisoc.org) to be included in this celebration. We hope to provide members not only a retrospective look back, but also a look at the future. Mark your calendars now for the meeting (July 12–16, 2008). You won't want to miss it.

The CRS BOD met September 6–8, 2007, at CRS headquarters in St. Paul, Minnesota. The BOD and senior staff members worked on the five-year CRS strategic plan. The BOD assessed where CRS is now and where it should be in five years. From that, goals were set to achieve the five-year vision. We then looked at roles and responsibilities to help define our actions and set some priorities as to what we need to accomplish this year. We will meet again in November in San Diego, California, to further refine the plan and finalize our priorities to deliver measurable results. The next step will be communicating the plan to the committees and membership, so you can expect to hear more about it in my next message to you.

Communication is key to our success, and many of you have indicated that communication needs to be improved. The BOD and staff have developed a plan to improve communication both across the various groups and with the CRS membership. The plan includes a BOD member contact for each committee. We hope that by having more timely and consistent communication between the BOD contact member and the committee chair we will improve the efficiency and effectiveness of our committee structure. We value the time and effort you, our volunteer members, give to these committees and hope to better direct and encourage committee activities so they can help meet the objectives of the strategic plan.

A second priority is redesigning the website so it is a more efficient and useful communication tool. The website will be a source for information on CRS and related activities and user friendly so people can find what they want or need. I have established an *ad hoc* web redesign committee to work with staff and have given them the goal of launching the redesigned website by the CRS Annual Meeting in New York City.

As Past President Randy Mrsny has explained in the past, we are moving thoughtfully down the path to rebrand the Controlled Release Society as CRS. CRS is the leading multidisciplinary society dedicated to promoting the science of delivery of bioactives for the benefit of the global population.

I would like to hear from you if you have suggestions. After all, this is your society. Have a great fall. ■

Journal of Controlled Release Highlights

By Kinam Park

The Impact Factor Impacting the Journal

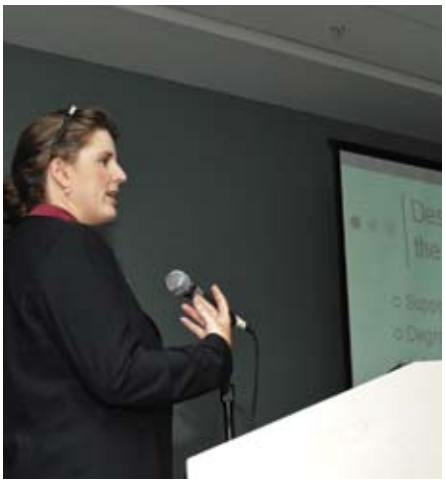
The impact factor has been used as a parameter evaluating the relative importance of various journals. The impact factor of the *Journal of Controlled Release* (JCR) in 2006 is 4.012. For the first time in the history of JCR, the impact factor increased over 4.0. The average number of articles published in JCR each year since 2001 is 270, except in 2005. The total number of articles published in 2005 was 434. This temporary surge was due to the publisher's efforts to clear up all backlogs so JCR could publish articles as fast as possible. The average manuscript processing time from submission to the final disposition to the publisher is 7.3 weeks. Our plan is to publish the articles within three months after submission by the author(s). We believe that it is highly important to minimize the publication time after a manuscript is received by the journal office.

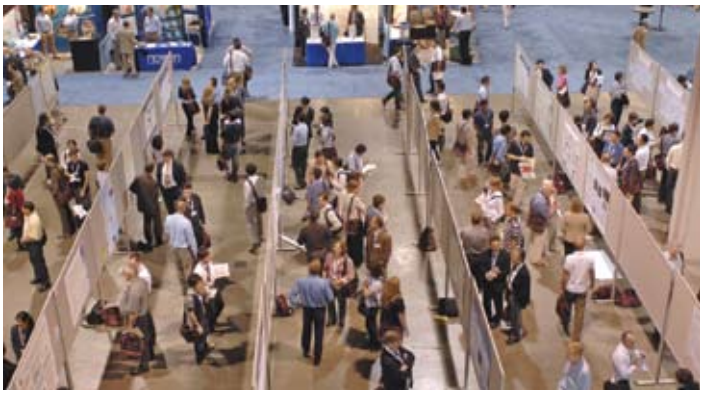
The editors of JCR strive to provide articles with current topics to the readers in a timely manner. Below is a list 10 articles that were the most cited in 2005. The highest number of citations for an article was 58. Each of the articles in the list describes the newest, most current research topics advancing new drug delivery technologies. Recently, the journal has been receiving many manuscripts related to nano/micro fabrication of drug delivery systems. As JCR continues to publish state-of-the-art research articles, we are cautiously optimistic that the impact factor in 2007 will continue to increase. With your help, JCR hopes to increase its impact factor to above 5 in the near future, and the editors of JCR thank the authors, reviewers, and readers of the journal.

Top 10 most cited articles published in 2005

1) Cationic TAT Peptide Transduction Domain Enters Cells by Macropinocytosis
2) Transmucosal Macromolecular Drug Delivery
3) Dual Growth Factor Delivery from Degradable Oligo(poly(ethylene glycol) fumarate) Hydrogel Scaffolds for Cartilage Tissue Engineering
4) Block Copolymer Micelles: Preparation, Characterization and Application in Drug Delivery
5) Microencapsulation by Solvent Extraction/Evaporation: Reviewing the State of the Art of Microsphere Preparation Process Technology
6) Multilayered Polyelectrolyte Films Promote the Direct and Localized Delivery of DNA to Cells
7) Biodegradable Polymer Microneedles: Fabrication, Mechanics and Transdermal Drug Delivery
8) PEG-Grafted Chitosan as an Injectable Thermosensitive Hydrogel for Sustained Protein Release
9) Polyethylenimine with Acid-Labile Linkages as a Biodegradable Gene Carrier
10) Doxorubicin Loaded pH-Sensitive Polymeric Micelles for Reversal of Resistant MCF-7 Tumor ■

Highlights of the 2007 CRS Annual Meeting & Exposition



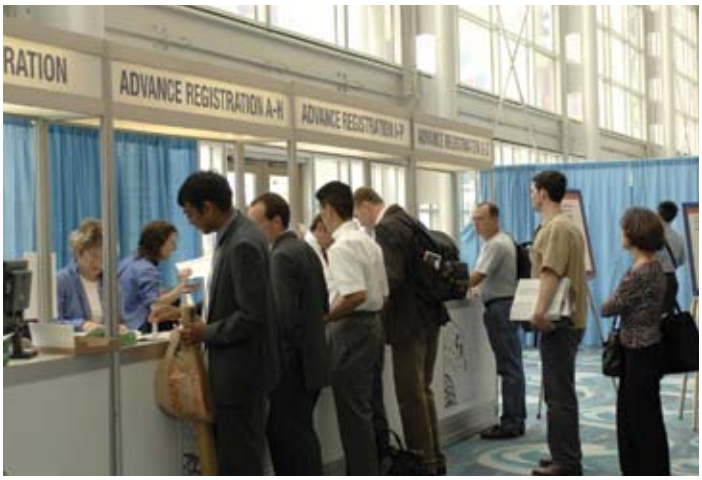



Injectable Drug Delivery
Nanospheres
PLGA
PEG-PLGA

Meeting Round-up

The cool ocean breezes set a relaxed and enjoyable tone for the 34th Annual Meeting & Exposition of the Controlled Release Society in Long Beach, California. The incredible science and exhibiting companies inside the Long Beach Convention Center kept everyone off the beaches and on the edge of their seats and walking the exhibit floor.

CRS Long Beach started off with a bang, offering three highly successful educational workshops on Saturday. The sell-out crowds in the Micro- and Nanoencapsulation: Formulation, Applications, and Processes (chaired by J. Chris Soper, Paul Richardson, and Ron Versic); Molecular Imaging and Drug Delivery (chaired by Alexei Bogdanov and Zheng-Rong Lu); and Sustained Release Parenteral Products: *In Vitro* and *In Vivo* Considerations (chaired by Marilyn Martinez and Mike Rathbone) Educational Workshops filled their rooms with outstanding presentations and Q&A sessions that continued long after the closing bells rang. The attendees of the micro- and nanoencapsulation workshop just couldn't get enough and spent another half day together on Sunday learning more about formulations, applications, and processes.



Farid Dorkoosh and Rod Walker chaired a one-day Young Scientist Workshop focused on the application basics of pharmaceutical sciences in drug delivery. The room was packed with young, and not so young, scientists eager to hear about diffusion, solubility, rheology, colloid chemistry, polymeric systems, and challenges in developing sustained release formulations from both academic and industrial points of view.

Together with members of the CRS Consumer & Diversified Products Committee, Farid and Rod once again had a young, captive audience on hand to hear introductions of various C&DP controlled release technologies. This Sunday morning session gave an overview of microencapsulation technologies used in the areas of personal care, flavor and fragrance, and industrial applications, along with fluid bed technology. Attendees also learned how to do IP searches in the field of controlled release technologies.

The companies presenting the Releasing Technology Workshops opened up their informational files on Sunday afternoon to enthralled audiences. Whether you attended Altea Therapeutics' presentation on "Transdermal Drug Delivery Through Microporated Skin," Colorcon's presentation on "Oral Extended Drug Release Based on Hydrophilic Polymers: Single and Multi-Unit Systems," Fuji HealthScience's presentation on "F-MELT: A Directly Compressible Excipient for Immediate Oral Release," ChemImage's presentation on "Hyperspectral Chemical Imaging for the Physical and Chemical Characterization of Drugs in Polymers," CMA/Microdialysis' presentation on "Microdialysis: Continuous *In Vivo* or *In Vitro* Drug & Target Collection," Genzyme Pharmaceuticals' "LipoBridge®: A Molecular Queen Mary for Crossing the BBB," or Capsugel's presentation on "Liquid Filled Two-Piece Capsules for Challenging Molecules," you came away with knowledge you could only acquire by being there at that time.

The Sunday Soapbox Session was standing-room-only, and for good reason. From the 40+ submissions received, Chairs Philippe Dor and Eyal Ron once again selected a great mix of presenters and topics for the five-minute pitches. Due to the popularity of the Soapbox, a first-ever Soapbox Session was held on Tuesday as the introduction to the Industrial Session.

The Sunday afternoon Highlights of Student Posters Session was chaired by Kurt Fegely of Colorcon, who along with Genencor International, have sponsored this session for the past three years. Ten students were selected from among 112 who applied. If you happened to miss this dynamic session, be sure to look for Jennyfer Cazares-Delgadillo, Ramesh Dandu, Esha Desai, Sanjay Gayakwad, Amit Kale, Todd Kaneshiro, Chen-Yu Kao, Venugopal Marasanapalle, Anna Mero, and Tri-Hung Nguyen's award-winning posters in the CRS Annual Meeting & Exposition's *Transactions* CD-Rom. Todd Kaneshiro received the top prize.

Nothing gets your blood boiling like a good debate. CRS had three Pearls of Wisdom debates running simultaneously on

Sunday afternoon; so if you saw Hamid Ghandehari running from room to room, it was because he was the Pearls chair once again. The bioactive materials topic, "Viral vs. Non-rival Gene Delivery," was one sided in John Chiorini's favor until Leaf Huang came rushing in saying that viral vectors are not superior to non-viral. The C&DP topic, "Nanotechnology: Economic Benefit or Potential Hazard," played out to a packed room, and it's been said that the debate continues on to this day among Chuck Frey, Alexander Kabanov, Andre Nel, and Neal Vail. The Vet topic, "*In Vitro* Drug Release Tests Are Invaluable Tools in Veterinary Product Development and Quality Control," shook up some of the traditional thoughts on testing. Which side did you favor—Avi Thombre's or Mike Rathbone's?

The rush was on Sunday evening to get to the Welcome Reception in the Exhibit and Poster Hall early and stay late. Plenty of nibbles and bits were consumed, exhibits visited, and posters viewed. The Exhibit and Poster Hall remained a popular venue throughout the annual meeting and exposition.

The Education Committee's Young Scientist Workshop Chairs Farid Dorkoosh and Rod Walker must not mind getting an early start to their day, along with a few of their closest 100 or so friends, because the Long Beach Get Up; Get Educated sessions on Monday and Tuesday mornings were very successful. On Monday, Raimar Loebenberg discussed "*In-vitro/In-vivo* Correlation"; and on Tuesday, Bryan Crist spoke on "The Basics of *In Vitro* Dissolution Testing."

The Welcome to CRS 2007 was kicked off on Monday with the grand Awards Ceremony, followed by the CRS Member Meeting. CRS is honored to be the premiere Society dedicated to controlled release and delivery technologies, and this was clearly evident at the Awards Ceremony. Winning one of the highly competitive CRS abstract-based and nominated awards is quite an achievement due to the quality and quantity of abstracts and nominees reviewed. CRS and the award sponsors congratulate all of the winners and thank all of the committee members who made the tough decisions.

The CRS Member Meeting provided a clear picture of where the Society is headed scientifically and the message that all is well financially. The meeting was full of goodbyes and thank yous as Board members Vladimir Torchilin, Martyn C. Davies, and Clive

Wilson, along with BSA members Todd Becker, Terry Bowersock, Karsten Cremer, Paul Gellert, and Elka Touitou, completed their terms of office.

David Tirrell, from the California Institute of Technology, was the first Plenary Speaker in Long Beach. Dr. Tirrell's presentation, "Non-Canonical Amino Acids in Protein Design, Evolution and Analysis," held everyone's attention.

The Industrial Sessions were as popular as ever, playing to standing-room-only crowds during the sessions held on Monday and Tuesday mornings and afternoons. Watch for Industrial Session Chair Ted Broman's new and innovative ideas for New York.

Monday afternoon brought award winners, Founders' Award winner Allan Hoffman and Young Investigator Award winner David Putnam, to the forefront. Hearing about why they were selected from the field of many and about their careers to date was a big hit with all in attendance.

Special sessions have been part of the CRS for years, and 2007 brought the Eurand Special Session on Monday and the Capsugel Special Session on Tuesday. These sessions hit on topics of interest and had the added excitement of the selection of their final award winners. The Eurand Grand Prize was awarded to Jouni Hirvonen. The Capsugel Innovative Award winner was Mayank Bhavsar.

The Vet Get Together is a tradition for those involved in the many veterinary and related fields. This year's gathering featured Terry Bowersock as the keynote speaker. Plenty of liquid refreshment was enjoyed by all, and it certainly got interesting discussions going and tall tales told.

Attendees were inspired on Tuesday morning by Steven Buchsbaum's plenary presentation, "Improved Childhood Vaccines—A Grand Challenge in Global Health." Scientists, clinicians, physicians, researchers, and academicians involved in controlled release and delivery are making a difference in lives, and Dr. Buchsbaum told CRS about many opportunities to positively impact the world.

Meeting Round-up continued on page 10

Meeting Round-up continued from page 9

A first for CRS was the mini-symposium, Recent Delivery in Diabetes, held jointly with the Juvenile Diabetes Research Foundation. This informative gathering was the brainchild of JDRF Program and Research Director Aaron Kowalski and CRS Scientific Secretary Martyn C. Davies. From the reaction of the audience, it's a wonderful thing that these two got together and discussed what could happen. Aaron, along with Julia Greenstein of the JDRF Immunology Programs and Strategic Partnerships, made it happen.

Tuesday afternoon's Plenary Session given by Teruo Okano on "Cell Sheet Tissue Engineering and Their Clinical Applications" was outstanding. Even when Prof. Okano's talk was over the crowd seemed to want more.

The Aquarium of the Pacific was the site for the CRS Closing Reception/Banquet. It was hard to tell who was more inquisitive—the aquatic life inside the glass walls or the humans with their funny faces staring into the undersea life on display. CRS President Randall Mrsny welcomed the diners and asked all to join in a salute to honor CRS pioneer Joe Robinson, who passed away in 2006. Since Joe was an avid fisherman, he would have appreciated being toasted while surrounded by hundreds of fish. Before dessert was served, Dr. Mrsny ceremoniously presented the Distinguished Service Award to Mike Rathbone, the Founders' Award to Allan Hoffman, and the Young Investigator Award to David Putnam. There was one more piece of official business that took place before the night with the fishes ended and that was witnessing Randall Mrsny hand the CRS gavel to incoming President Susan Cady. It was a delightful way to conclude a lovely evening.

In the past, after enjoying a CRS banquet on a Tuesday night there have been some attendees who have not quite made it to the plenary presentation the following morning. This was definitely not the case this year. Dr. Joseph M. DeSimone spoke to an alert and involved group. His presentation on "Organic Delivery Vehicles for Probing and Treating Biological Systems: Adapting Fabrication Processes from the Electronics Industry for Use in Nanomedicine" had everyone ready for the full day ahead.

As Wednesday afternoon came around, you could feel the anticipation of the final plenary presentation of the meeting. Patrick Soon-Shiong's presentation, "The Role of Biomarkers and Biologically Interactive Delivery Systems (Receptor Mediated Transcytosis) in the Future of Chemotherapy," met everyone's expectations. The time Dr. Soon-Shiong devoted to answering questions was truly appreciated.

A CRS Annual Meeting & Exposition wouldn't be complete without the outstanding science, exhibitors you need to talk with, committee meetings to attend, catching up with old friends and making new friends, developing plans to complete ongoing projects and new ideas, and just having a grand time. It's with these thoughts in mind that the door closes on Long Beach and opens wide to New York! See you there. ■

Brought to You By

Many thanks to the following CRS volunteers for their time and talents in bringing us the 34th Annual Meeting & Exposition of the Controlled Release Society in Long Beach, California, July 7-11, 2007:

Scientific Secretary
Martyn C. Davies
University of Nottingham, U.K.

Bioactive Materials Track Program Co-Chairs
You Han Bae, University of Utah, U.S.A.
Alexander Kabanov, University of Nebraska Medical Center, U.S.A.
Derek O'Hagan, Novartis Vaccines & Diagnostics, Italy

Consumer and Diversified Products Program Co-Chairs
Charles Frey, Coating Place, Inc., U.S.A.
Douglas Dale, Genencor, A Danisco Division, U.S.A.

Veterinary Program Co-Chairs
Craig Bunt, AgResearch, New Zealand
Sevda Senel, Hacettepe University, Turkey

Educational Workshop Chairs
Alexei Bogdanov, University of Massachusetts, U.S.A.
Zheng-Rong Lu, University of Utah, U.S.A.
Marilyn Martinez, FDA Center for Veterinary Medicine, U.S.A.
Michael Rathbone, InterAg, New Zealand
Paul Richardson, Balchem Corporation, U.S.A.
J. Chris Soper, Givaudan Flavours, U.S.A.
Ronald Versic, Ronald T. Dodge Co., U.S.A.

Industrial Session Co-Chairs
Ted Broman, Vivus, Inc., U.S.A.
Susan Cady, Intervet, Inc., U.S.A.
David Friend, Consultant, U.S.A.

Lunch with the Experts Chair
Chun Wang, University of Minnesota, U.S.A.

Pearls of Wisdom Session Chair
Hamid Ghandehari, University of Maryland, U.S.A.

Releasing Technology Workshop Chair
Martyn C. Davies, University of Nottingham, U.K.

Soapbox Session Co-Chairs
Philippe J.M. Dor, MacuSight, Inc., U.S.A.
Eyal S. Ron, MADASH, LLC, U.S.A.

Education Committee/Young Scientist Events
Farid Dorkoosh (co-chair), Synthon, BV, The Netherlands
Michael J. Rathbone (co-chair), InterAg, New Zealand
Roderick B. Walker, Rhodes University, South Africa

Awards Coordinating Committee
Lisbeth Illum (chair), IDentity, U.K.
Michael J. Calandra, Firmenich, Inc., U.S.A.
William N. Charman, Monash University, Australia
Duncan Q. Craig, University of East Anglia, U.K.
David W. Grainger, III, University of Utah, U.S.A.
Jorge Heller, Consultant, U.S.A.
Vinod D. Labhasetwar, Cleveland Clinic Foundation, U.S.A.
Claudia S. Leopold, University of Hamburg, Germany
Hans E. Junginger, Naresuan University, Thailand
Sevda Senel, Hacettepe University, Turkey
Ronald A. Siegel, University of Minnesota, U.S.A.

The Controlled Release Society Thanks the 34th Annual Meeting & Exposition Sponsors

Recognizing Excellence

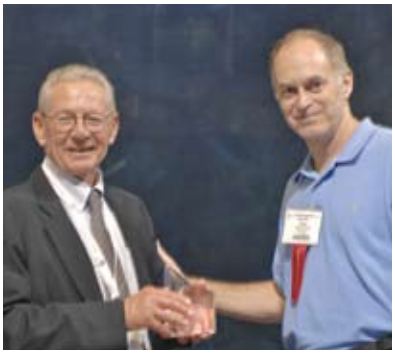
Congratulations 2006 and 2007 CRS Awardees!

The Controlled Release Society's Awards Ceremony held during the 34th Annual Meeting & Exposition in Long Beach, California, was a special affair that honored scientists from around the globe. The CRS is grateful to the many sponsors who provided their time and financial support to promote the talented scientists and innovative science that were highlighted at the meeting. Congratulations to all!

2007 Student Posters Award winners: Jennyfer Cazares-Delgadillo, Ramesh Dandu, Esha Desai, Sanjay Gayakwad, Amit Kale, Todd Kaneshiro, Chen-Yu Kao, Venugopal Marasanapalle, Anna Mero, and Tri-Hung Nguyen. The award is co-sponsored by Colorcon and Genencor International, Inc.

Kristy M. Ainslie, Mayank Bhavsar, Kathleen Fischer, and Xin-Ming Liu are each honored with the 2007 Innovative Aspects of Oral Drug Delivery and Absorption Graduate/Post-Doc Award, co-sponsored by Capsugel, from Dennis Murachanian of Capsugel.

Michael J. Rathbone receives the 2007 CRS Distinguished Service Award from CRS President Randall Mrsny.



Allan Hoffman receives the 2007 CRS Founders' Award from CRS President Randall Mrsny.

David Putnam receives the 2007 CRS Young Investigator Award from CRS President Randall Mrsny.

Jeong Woo Lee receives the 2006 Outstanding Paper in Drug Delivery Award, co-sponsored by 3M Drug Delivery Systems, from Richard Sitz of 3M Drug Delivery Systems.

Tae Hee Kim receives the 2006 Outstanding Pharmaceutical Paper Award, co-sponsored by Banner, from Aqeel A. Fatmi of Banner.

Keith J. Ellis receives the 2006 Outstanding Veterinary Paper Award, co-sponsored by Intervet, from Susan Cady of Intervet.

Karsten Maeder accepts the 2007 Outstanding Consumer & Diversified Products Paper Award, co-sponsored by Firmenich, from Birgit Schleifenbaum of Firmenich on behalf of Christian Augsten and Andreas Huenerbein.

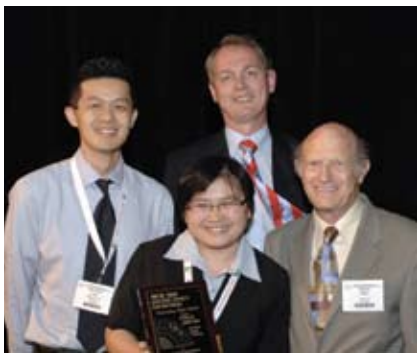
Kathleen Fischer receives the 2007 CRS Outstanding Oral Drug Delivery Paper Award from CRS President Randall Mrsny.

Lisbeth Illum receives the 2007 Career Achievement in Oral Drug Delivery Award, co-sponsored by Eurand, from Stephen Perrett of Eurand.

John S. Patton receives the 2007 Nagai Innovation Award, co-sponsored by the Nagai Foundation Tokyo, from Tsuneji Nagai of the Nagai Foundation Tokyo.

Jouni Hirvonen receives the 2007 Novel Approaches in Industrial Oral Drug Delivery Award, co-sponsored by Eurand, from Stephen Perrett of Eurand. Andreas Bernkop-Schnuerch also was honored with the award.

Paolo Colombo receives the 2007 Rainer Hoffmann Product Through Science Award, co-sponsored by Lohmann Therapie-Systeme AG, from Hans Junginger, chair of the Rainer Hoffmann Product Through Science Award Committee and Werner Wessling of Lohmann Therapie-System AG.



Yi-Ping Ho and Hunter H. Chen receive the 2006 Jorge Heller Journal of Controlled Release Outstanding Paper Award, co-sponsored by Elsevier, from Jaap vanHarten of Elsevier and Jorge Heller, the award's namesake.

Thank you to the Exhibitors of the 34th Annual Meeting & Exposition of the Controlled Release Society!

More than 100 exhibiting companies offered the latest research, technology, products, and services for controlled release and delivery at the Long Beach, California, meeting.

3M Drug Delivery Systems
Activaero America, Inc.
Adhesives Research
Alkermes, Inc.
Allergan, Inc.
Almac Pharma Services
Altea Therapeutics Corporation
Aptuit, Inc.
Aqualon, A Business Unit of Hercules
Asahi Kasei Chemicals Corporation
Avanti Polar Lipids, Inc.
Azopharma
Banner
BASF Corporation
Baxter Healthcare Corporation
Bilcare, Inc.
Bio-Images Research Ltd.
Biovail Contract Research
Boehringer Ingelheim
BRACE GmbH
Brookwood Pharmaceuticals
Buchi Corporation
Capsulution NanoScience AG
Catalent Pharma Solutions
Carpe Diem, A Wiley Company
ChemAgis USA, Inc.
ChemImage Corp.
CMA/Microdialysis, Inc.
Coating Place, Inc.
Colorcon, Inc.
CyDex Inc.
Degussa Pharma Polymers
Depomed, Inc.
Dissolution Technologies
Distek, Inc.
DPT Laboratories
Dr. Reddy's Laboratories, Inc.
Drug Delivery
Duoject Medical Systems Inc.
DURECT Corporation – LACTEL® Absorbable Polymers
Elan Drug Technologies
Elsevier
ERWEKA GmbH
FMC Corporation
Gaylord Chemical Corporation
Genzyme Pharmaceuticals
Glatt Pharmaceutical
Halozyme Therapeutics
Hanson Research
Hisamitsu Pharmaceutical Co., Inc.
Horiba Instruments, Inc.
Hovione
ICON Development Solutions
Imaginot Pty. Ltd.
Inabata America Corporation/ Nippon Fine Chemical
Informa Healthcare
Innojet Technologies
Inotech Biosystems International
International Specialty Products
IOMED, Inc.
Irvine Pharmaceutical Services
LCI Corporation
Lipoid LLC
LTS Lohmann Therapy Systems
Malvern Instruments
Microfluidics Corporation
Molecular Profiles Limited
Mylan Technologies Inc.
Northern Lipids Inc.
NovaMatrix
Noven Pharmaceuticals, Inc.
Noveon, Inc.
Oakwood Laboratories, L.L.C.
OctoPlus
O'Hara Technologies
ONdrugDelivery Ltd.
Oxford Instruments
Patheon Inc.
Penn Pharmaceutical Services Ltd.
Pharma Test Americas, Inc.
Pharmaceutical Profiles
Pharmaceutical Technology
PharmaCircle, LLC
Phoqus Pharmaceuticals Limited
PII PolyMicrospheres – Advanced Nanotech
Polymun Scientific Immunbiologische Forschung GmbH
PURAC Biomaterials
Scintipharma, Inc.
SCOLR Pharma, Inc.
Shin-Etsu Chemical Co. Ltd./ Biddle Sawyer Corp.
Simulations Plus, Inc.
SOLIQS
SOTAX Corporation
Southwest Research Institute
SPI Pharma
Surface Measurement Systems
SurModics
Sympatec Inc.
Symyx Technologies, Inc.
Technology Catalysts International
TeraView
Texture Technologies Corp.
TheraJect, Inc
Travanti Pharma Inc.
Varian, Inc.
Vector Corporation

For 2008 exhibit information go to http://www.controlledreleasesociety.org/meeting/exhibitors/forExhibitors.cfm or contact Debby Woodard at +1.651.994.3817 or dwoodard@scisoc.org.

35th Annual Meeting & Exposition of the Controlled Release Society

Responding to Global Needs through Delivery Science

July 12–16, 2008
Hilton New York • New York, New York

Featured Plenary Speakers

Dora Akunyili, National Agency for Food and Drug Administration and Control, Nigeria
Topic to Be Announced

Mark E. Davis, California Institute of Technology, U.S.A.
Nanoparticle Cancer Therapeutics: From Concept to Clinic

Rakesh Jain, Massachusetts General Hospital & Harvard University, U.S.A.
Normalization of Tumor Vasculature and Microenvironment by Antiangiogenic Therapies: From the Bench to the Bedside and Back

Thomas Tuschl, Rockefeller University, U.S.A.
Mechanisms of Mammalian Small-RNA-Mediated Gene Regulation

Jackie Ying, Agency for Science, Technology, and Research, Singapore
Topic to Be Announced

Coming Soon to the Website

Call for Abstracts & Awards • Registration • Exhibits • Preliminary Program

www.controlledreleasesociety.org/meeting

Special Feature

Biomarkers—Fuelling a Revolution in Drug Development

By Dr. Louise Rosenmayr-Templeton
Tower Pharma Consulting, Vienna, Austria
Tel/Fax: +43 1 600 3464
E-mail: louise.templeton@towerpharmacon.com
Website: www.towerpharmacon.com

The use of biomarkers to study the clinical progression of disease and its treatment is set to revolutionise the way drug development is carried out. This article provides an overview of the scientific, clinical, economic, and political drivers behind the focus on biomarker research and what opportunities lie ahead if technical and regulatory hurdles can be overcome.

A biomarker has been defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (1). This definition encompasses both physical measurements, e.g., blood pressure readings, and the quantification of particular body constituents. In some cases it may not be the level of one biomarker that differentiates between health and disease, but changes in the profile or pattern of many.

Of course the exploitation of biomarkers to monitor disease and its therapy is not new, and numerous established examples exist, e.g., serum creatinine and HbA1C (glycosylated haemoglobin). What is new is that biomarkers are being actively sought with the aim of eventually validating them as indicators of disease progression, treatment efficacy or toxic effects. This search is driven by a number of factors:

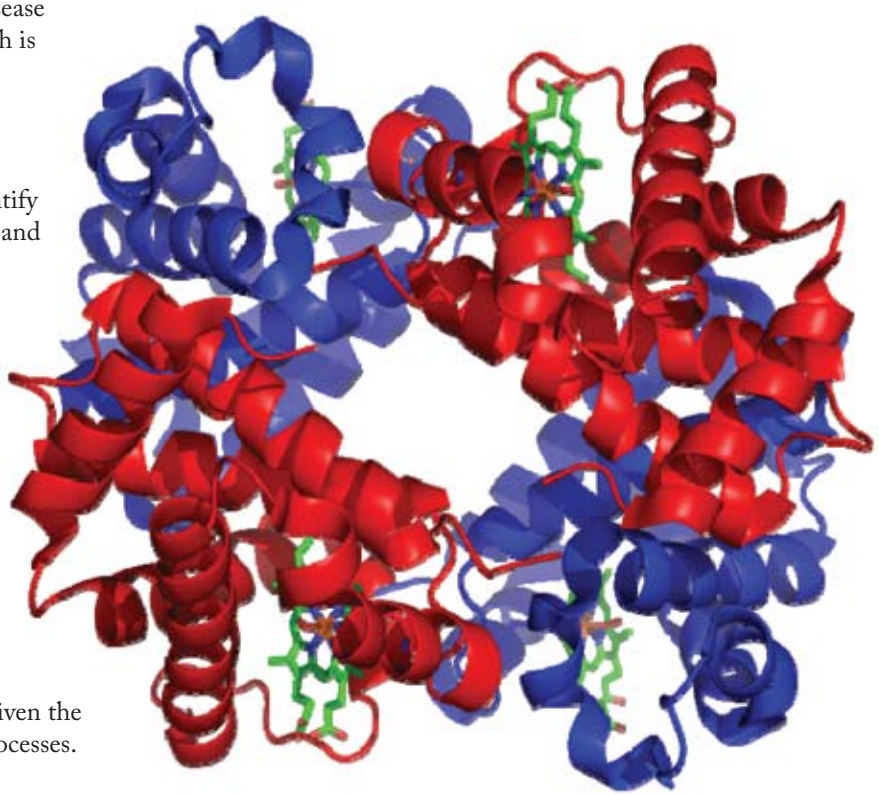
1) **Technical Advances and the Rise of "-omic" Technologies**
Scientists now have the technological means to identify and evaluate biomarkers at the genomic, proteomic, and metabolic levels. Advances in high-throughput molecular biology techniques, bioinformatics, and computational biology (2–4) mean that data can be generated, processed, and analysed in ways and at speeds that were only dreamt of previously.

These technological advances, in conjunction with traditional techniques such as mass spectroscopy and NMR, have provided the basis for newer "-omic" technologies. The study of messenger RNA (transcriptomics) provides a snapshot of which genes are active at a given time, while proteomics evaluates the proteins present and takes into account post-translational changes. Proteomics is considered an especially rich source of biomarkers given the role of proteins in physiological and pathological processes.

In addition, metabolomics (the systematic study of metabolites) has the potential to yield biomarkers, particularly for drug and toxicity monitoring purposes.

2) **Partnered Research Initiatives and Open Access to Databases of Basic Genomic Data**
The identification of new biomarkers is facilitated by scientists having open access to fundamental and enabling research into the genome in an easily searchable form. Databases of genomic data include those held by the European Molecular Biology Laboratory and the DNA Database of Japan.

Open access to data often arises as the result of fundamental research being funded by joint initiatives between government agencies, research trusts, academia, industry, and combinations thereof. For example, it is envisaged that data from the HapMap Project and the SNP Consortium (5) will assist scientists in identifying which haplotypes (patterns of single nucleotide polymorphisms) correlate with susceptibility to particular diseases.



3) The Drive to Meet Clinical Unmet and Half-Met Needs

The incidence of common diseases, such as Type 2 diabetes, cancer, and asthma, is increasing due to aging populations, lifestyle, and environmental factors. However, the aetiology of many such conditions, together with the factors that result in clinical progression or remission, remain unknown. The identification of specific biomarkers is a key component in improving the understanding, diagnosis, monitoring, and imaging of many diseases (6,7). Ultimately, it is hoped that such research will lead to diagnostic tests for pre-symptomatic diagnosis and more effective, and perhaps curative, treatments. It is not surprising, therefore, that biomarker research features heavily in many academic and industrial research programmes (7–11).

4) Development Cost Containment—Improving Clinical Candidate Selection

Drug development costs are soaring, and since clinical research accounts for a large chunk of the budget, there is an urgent need to reduce the current 80–90% candidate failure rate during clinical testing (10). Biomarker identification and validation could potentially improve clinical candidate selection and increase the efficiency of clinical research by

- Improving the understanding of basic disease mechanisms and facilitating the development of animal models predictive of efficacy and/or toxicity.
- Enabling the selection of patients who are likely to have a positive clinical response based on genetic traits and, thus, reducing the risk of clinical failure.
- Being a key research tool in translational research relating laboratory results to clinical findings and vice versa.
- Acting as surrogate markers for clinical efficacy and, therefore, shortening the time to regulatory submission.

5) Economic and Political Concerns about Medical Innovation and Competitiveness

Political and commercial interest in biomarkers lies in their role in developing innovative, effective healthcare and their potential to increase the efficiency of drug development and, hence, encourage investment and economic competitiveness at both corporate and national levels. As previously stated, governments and industry are investing millions in biomarker research, both alone and as part of public–private partnerships (7–11). The economic importance of this research is illustrated by its prominence in strategy documents such as the U.S. FDA's Critical Path Initiative (8,10) and the EU's Innovative Medicines Initiative (7).

Challenges Ahead

As can be seen from the above discussion, biomarker research is set to play a major role in improving the effectiveness and efficiency of drug development. However, the technical hurdles to be overcome should not be underestimated. For example, correlating haplotypes with disease susceptibility or clinical response is no small matter, while proteomics yields far more complex, variable data than that obtained from the genome. In addition, a great deal of basic research is still required, and the use of genomic data in clinical research is still in its infancy. At the regulatory level only limited guidance exists on the use and validation of biomarkers for clinical decision-making purposes (12), and it is evolving. However, the active involvement of regulatory authorities in research-based initiatives (7,8,10), their readiness to agree on common definitions for pharmacogenomic terms (13), and their encouragement of voluntary submission of genomic data (14) illustrate the importance they place on biomarkers in future drug development.

In summary, if technical and regulatory challenges can be overcome, biomarkers may radically alter our approach to drug development and pave the way for the personalised medicines of the 21st century.

References

1. Biomarkers Definition Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework, Clin. Pharm. Ther. 69: 89-95 (2001).
2. Csako, G. Present and future of rapid and/or high-throughput methods for nucleic acid testing, Clin. Chim. Acta 363(1-2): 6-31 (2006).
3. Bertone, P, Snyder, M. Advances in functional protein microarray technology. FEBS J. 272(21): 5400-5411 (2005).
4. Teufel, A, Krupp, M, Weinmann, A, Galle, PR. Current bioinformatics tools in genomic biomedical research (Review), Int. J. Mol. Med. 17(6): 967-973 (2006).
5. HapMap Project. http://www.hapmap.org/ (2007).
6. Maruvada, P, Wang, W, Wagner, PD, Srivastava, S. Biomarkers in molecular medicine: Cancer detection and diagnosis. Biotechniques April(Suppl.): 9-15 (2005).
7. Innovative Medicines Initiative. Research agenda of the Innovative Medicines Initiative. Published online at www.imieurope.org/Publications.aspx?vi<ewCategory=Researchx20Agenda (2007).
8. FDA. Critical path opportunities report. Published online at http://www.fda.gov/oc/initiatives/criticalpath/ (2006).
9. GlaxoSmithKline. Genetics at GSK. Published online at http://genetics.gsk.com/geneticsatgsk.htm (2007).
10. FDA. Challenge and opportunity on the critical path to new medical products. Published online at http://www.fda.gov/oc/initiatives/criticalpath/ (2004).
11. Wyeth Pharmaceuticals. Wyeth Pharmaceuticals announces Scottish collaboration to enhance translational medicine research. Published online at http://www.wyeth.com/news (2006).
12. Frueh, F. Clarifying the current regulatory position on the validation and standardization of biomarkers for approval and ongoing patient care. Published online at http://www.fda.gov/cder/genomics/presentations.htm (2007).
13. International Conference on Harmonisation. Final Concept Paper E15: Terminology in pharmacogenomics. Published online at http://www.ich.org/cache/compo/276-254-1.html (2006).
14. FDA. Voluntary genomics data submission (VGDS). Published online at http://www.fda.gov/cder/genomics/VGDS.htm (2007).

Scientifically Speaking

Biodegradable Nanoparticles for Vaccine Adjuvants and Delivery Systems

By Takami Akagi, Department of Applied Chemistry, Osaka University, and CREST JST, Japan; Masanori Baba, Division of Antiviral Chemotherapy, Center for Chronic Viral Diseases, Kagoshima University, and CREST JST, Japan; and Mitsuru Akashi, Department of Applied Chemistry, Osaka University, and CREST JST, Japan
Tel: +81-6-6879-4129; Fax: +81-6-6879-7359
E-mail: akagi@chem.eng.osaka-u.ac.jp

Introduction

Biodegradable polymeric particles, especially nanoparticles, have attracted considerable attention as potential drug controlled delivery devices to deliver low molecular weight drugs, as well as biomacromolecules such as proteins or DNA. In particular, polymeric nanoparticles with entrapped antigens represent an exciting approach to control the release of vaccine antigens and to optimize the desired immune response via selective targeting of the antigen to antigen-presenting cells (APCs) (1). The submicron size range of these delivery systems offers a number of distinct advantages over microparticles, including relatively higher intracellular uptake compared with microparticles.

Dendritic cells (DCs) are highly specialized APCs that can activate native T cells and, hence, initiate primary immune responses. DCs are found in epithelial and mucosal tissues, where they take up and process antigens through major histocompatibility complex (MHC) class I and II pathways and initiate immunity by antigen-specific stimulation of T cells. Therefore, the delivery of antigens to DCs and the activation of the antigen-presenting pathway are two of the most important issues in the development of effective vaccines. Moreover, adjuvants that possess the ability to induce DC maturation are useful for DC-based immunotherapy.

Biodegradable polymers based on poly(lactic-*co*-glycolic acid) (PLGA) are fully biocompatible and, therefore, among the most common materials used for encapsulating therapeutic agents. PLGA micro/nanoparticles have been used for the delivery of antigens and the stimulation of immune responses (2). Antigen-loaded PLGA nanoparticles are generally formulated using the emulsion solvent evaporation method. There are major problems associated with this method, however, including low encapsulation efficiency of highly water-soluble proteins and instability arising during the formulation, storage, degradation, and lyophilization of the nanoparticles. Therefore, there is a need to develop alternative nanoparticles that can overcome such defects of polyester-based materials.

To this end, we have designed a novel protein delivery system with self-assembled amphiphilic polymeric nanoparticles (3). Amphiphilic block or graft copolymers consisting of hydrophilic and hydrophobic segments are self-assembling materials and are capable of forming polymeric associates in aqueous solutions. Several amphiphilic copolymers based on poly(amino acid) have been employed, such as poly(L-glutamic acid), poly(L-aspartic acid), poly(L-lysine), poly(L-arginine), poly(L-asparagine), and poly(γ-glutamic acid) as hydrophilic segments and poly(β-benzyl-L-aspartate), poly(γ-benzyl-L-glutamate), and poly(L-histidine) as hydrophobic segments. These amphiphilic copolymers form micelles through self-association in water. Hydrophobic blocks form the inner core of the structure, acting as an incorporation site for therapeutic agents, especially for hydrophobic drugs.

In this study, we selected poly(γ-glutamic acid) (γ-PGA) as the biodegradable hydrophilic polymer and hydrophobic amino acid (HAA) as the hydrophobic side chain (4). γ-PGA is composed of naturally occurring D- and L-glutamic acid γ-linked together through amide bonds. The α-carboxylate side chains of γ-PGA can be chemically substituted to introduce various molecules. Here we repost the use of nanoparticles composed of amphiphilic γ-PGA as vaccine adjuvants (5).

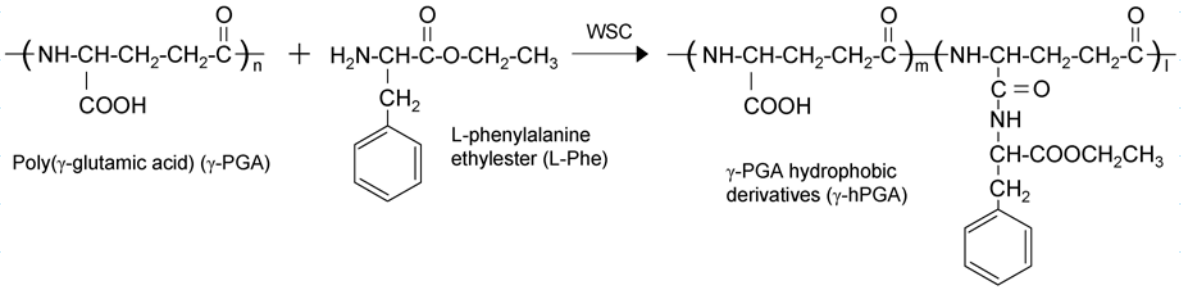


Figure 1. Synthesis of γ-PGA hydrophobic derivatives (γ-hPGA).

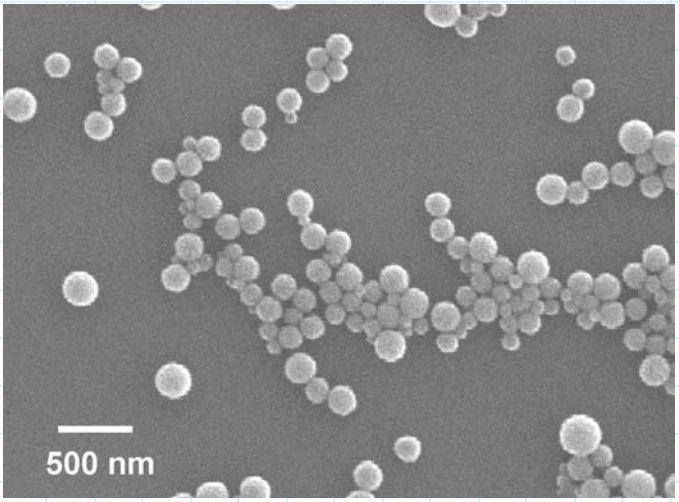


Figure 2. SEM images of γ-hPGA nanoparticles.

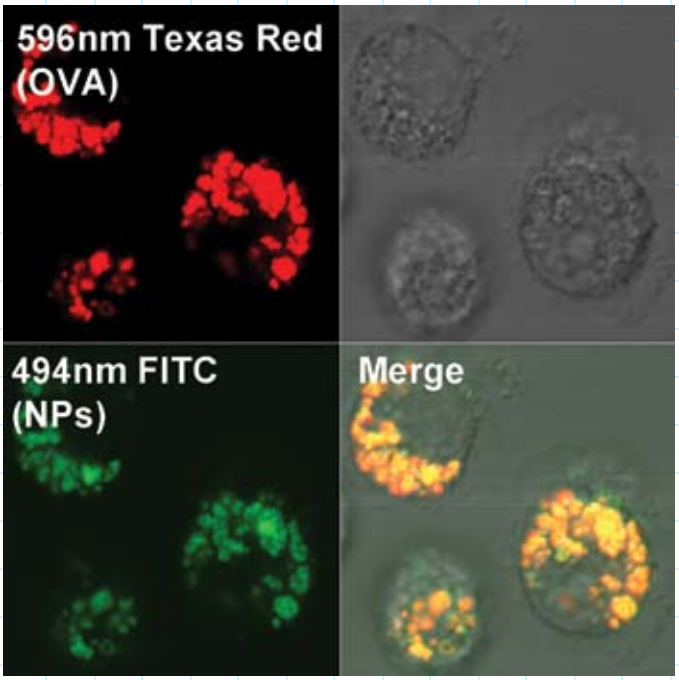


Figure 3. CLSM images of iDCs pulsed with TR-OVA/FITC-NPs. Co-localized regions of OVA (red) and NPs (green) appear yellow.

Preparation of γ-hPGA Nanoparticles and Protein-Loaded Nanoparticles

γ-PGA hydrophobic derivatives (γ-hPGA) were synthesized by the conjugation of L-phenylalanine ethylester (L-Phe) (Figure 1). γ-hPGA nanoparticles were prepared using a precipitation and dialysis method. First, the γ-hPGA (10 mg) was dissolved in 1 mL of DMSO, and saline at the same volume was added to yield a translucent solution. The solutions were then dialyzed against distilled water to remove the organic solvents. γ-hPGA with more than a 40% degree of grafting could form 200-nm nanoparticles due to its amphiphilic characteristics (Figure 2). To prepare the protein-encapsulated γ-hPGA nanoparticles, γ-hPGA (10 mg/mL in DMSO) was added to the same volume of ovalbumin (OVA) solution (2 mg/mL). The resulting solution was centrifuged and repeatedly rinsed. OVA was successfully encapsulated into the nanoparticles. The encapsulation efficiency of OVA in the γ-hPGA nanoparticles was approximately 50 wt.%.

Uptake of Protein-Loaded Nanoparticles by iDCs

To evaluate the uptake of OVA-encapsulated γ-hPGA nanoparticles (OVA-NPs) by DCs, murine bone marrow-derived immature DCs (iDCs) were incubated with Texas Red-labeled OVA (TR-OVA) encapsulated FITC-labeled NPs (TR-OVA/FITC-NPs). The cells then were analyzed with a confocal laser scanning microscope (CLMS). The CLSM images demonstrated that iDCs incubated with OVA-NPs efficiently internalized both OVA and NPs. Co-localization signals of OVA (red) and NPs (green) were observed inside the cells exposed to TR-

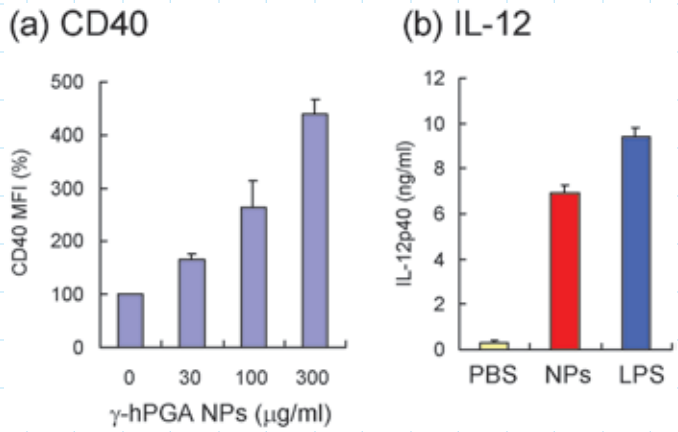


*Figure 4. Maturation of DCs induced by γ-hPGA nanoparticles. **A**, Enhanced expression of CD40 on the surface of DCs after NP uptake. **B**, Cytokine (IL-12) production by NP-pulsed DCs.*

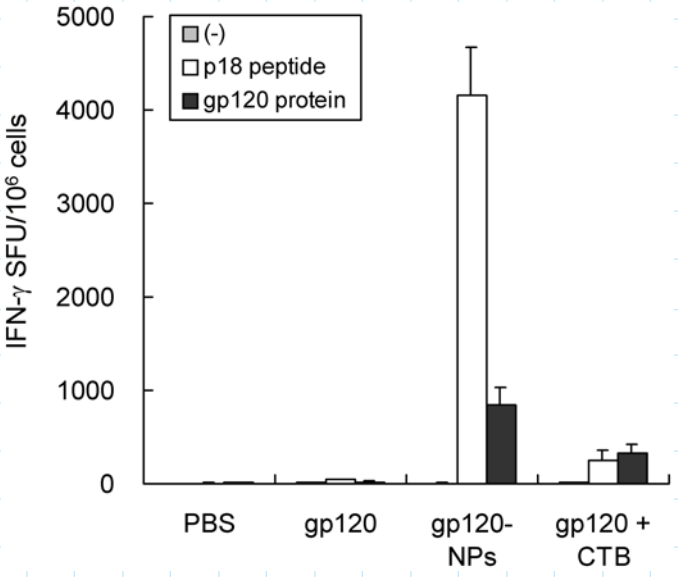


Figure 5. Induction of cellular immunity by intranasal immunization with HIV-1 gp120-NPs. The number of IFN-γ–producing cells was measured by ELISPOT.

Scientifically Speaking continued on page 20

Scientifically Speaking continued from page 19

OVA/FITC-NPs (Figure 3). These results indicate that γ-hPGA nanoparticles are efficiently taken up by iDCs and that the encapsulated protein can be co-delivered with nanoparticles to the iDCs.

Maturation of DCs Through Uptake of Nanoparticles

To determine whether the uptake of nanoparticles mediates the phenotypic and functional maturation of DCs, iDCs were incubated with γ-hPGA nanoparticles for 48 hr, and the expression of surface molecules and the production of cytokines were measured. As a positive control, iDCs were also incubated with LPS. NP-pulsed DCs displayed a marked increase in CD40, CD86, and MHC class I expression on their surface in a dose-dependent manner (Figure 4A). Moreover, significant amounts of IL-12, IL-1β, and TNF-α were detected in the culture supernatant of NP- and LPS-pulsed DCs (Figure 4B). These results suggest that γ-hPGA nanoparticles have great potential as adjuvant for DC maturation. Similar results were obtained with PLGA nano/microparticles, liposomes, cationic polystyrene microparticles, and acid-degradable cationic nanoparticles.

Induction of Cellular Immunity by HIV-1 gp120-Loaded Nanoparticles

Immune responses were investigated in BALB/c mice after intranasal immunization with HIV-1 gp120-encapsulated γ-hPGA nanoparticles (gp120-NPs). To determine the induction of cellular immunity, female mice were intranasally immunized once with gp120 alone, gp120-NPs, or gp120 + cholera toxin B subunit (CTB). Splenocytes from the mice immunized with gp120-NPs were examined for their ability to induce IFN-γ–producing cells using ELISPOT assays. Figure 5 shows that the mice immunized with gp120-NPs resulted in the efficient induction of IFN-γ–producing cells. These results indicate that the nanoparticles have the ability to prime cellular immunity by mucosal immunization.

Conclusions

Protein-encapsulated γ-hPGA nanoparticles could enhance protein delivery to iDCs. These γ-hPGA nanoparticles also had adjuvant activity for DC maturation. Thus, γ-hPGA nanoparticles have significant potential as an antigen carrier and adjuvant for DCs. Moreover, vaccination with antigen-encapsulated γ-hPGA nanoparticles dramatically enhanced cellular immunity. This system provides a novel delivery tool and efficient antigen delivery and adjuvant systems in the development of protein-based vaccines.

References

1. Panyam, J, Labhasetwar, V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue, Adv. Drug Deliv. Rev. 55: 329-347 (2003).
2. Jiang, W, Gupta, RK, Deshpande, MC, Schwendeman, SP. Biodegradable poly(lactic-co-glycolic acid) microparticles for injectable delivery of vaccine antigens, Adv. Drug Deliv. Rev. 57: 391-410 (2005).
3. Akagi, T, Kaneko, T, Kida, T, Akashi, M. Preparation and characterization of biodegradable nanoparticles based on poly(γ-glutamic acid) with L-phenylalanine as a protein carrier, J. Control. Release 108: 226-236 (2005).
4. Akagi, T, Wang, X, Uto, T, Babab, M, Akashi, M. Protein direct delivery to dendritic cells using nanoparticles based on amphiphilic poly(amino acid) derivatives, Biomaterials 28: 3427-3436 (2007).
5. Uto, T, Wang, X, Sato, K, Haraguchi, M, Akagi, T, Akashi, M, Baba M. Targeting of antigen to dendritic cells with poly(γ-glutamic acid) nanoparticles induce antigen-specific humoral and cellular immunity, J. Immunol. 178: 2979-2986 (2007). ■

Scientifically Speaking

Non-covalent Delivery of Peptide-Bound Drug into Multidrug-Resistant Leukemia Cells

By Zhaohua Zheng, Harmesh Aojula, and David Clarke
School of Pharmacy & Pharmaceutical Sciences
The University of Manchester, Manchester, UK

Tumor cells often become cross-resistant to many structurally and functionally different anti-cancer drugs. Such multidrug resistance (MDR) is recognized as a major obstacle to the success of chemotherapy in the clinic. One of the commonly accepted mechanisms of MDR is the over expression of certain ATP-binding cassette (ABC) transporter proteins, which reduce intracellular drug accumulation by pumping drugs out of cells, thus compromising drug efficacy. Moreover, these proteins are found in some of the subcellular compartments, sequestering drugs away from their intracellular targets in the cytoplasm. ABC transporter proteins include the multidrug-resistance protein (MRP), the lung-resistance protein (LRP), and the most-characterized P-glycoprotein (P-gp). P-gp, a 170-kDa glycoprotein encoded by the human ABCB1 (MDR1) gene, recognizes and transports many different substrates, including most commonly used anti-cancer drugs, including doxorubicin, vincristine, paclitaxel, teniposide, camptothecins, and cisplatin (1).

Delivery systems have been designed to enhance cellular accumulation and overcome MDR by uptake into cells via endocytosis to minimize contact between drug and P-gp at the inner leaflet of the cell membrane (Figure 1).

Generally covalently-bound drug-polymer conjugates are used. The cell-penetrating peptide Tat conjugated to doxorubicin also accumulates rapidly in resistant cells with minimal efflux by P-gp, promoting potent cytotoxicity (2). However, covalent conjugation of drug to peptide and polymer carriers modifies the drug and requires a mechanism (e.g., enzymatic) to cleave drug conjugated to the carrier. Non-covalent association between MDR drugs and carriers would avoid this problem, but such associations are often weak, resulting in premature leaching of the carried drug. Strong binding of drugs is often achieved by their receptors and target sites. The affinity for binding of a non-covalent drug carrier would ideally be weaker than to the target, but strong enough to retain the drug until the associated drug carrier reaches the target.

Peptides have the ability to bind drugs non-covalently through hydrophobic interaction (3). Constructed from a drug-binding motif (DBM) and the cell-penetrating peptide Tat, a hybrid peptide (DBM-Tat) has been produced to traffic MDR drugs (e.g., doxorubicin) into cells via endocytosis and to provide an intracellular drug depot.

The relative affinity for binding of doxorubicin (Dox) between the hybrid DBM-Tat and its DNA target was assessed by DNA displacement assay (Figure 2). Approximately 1 molecule of Dox was bound by every 10 molecules of DNA at saturation

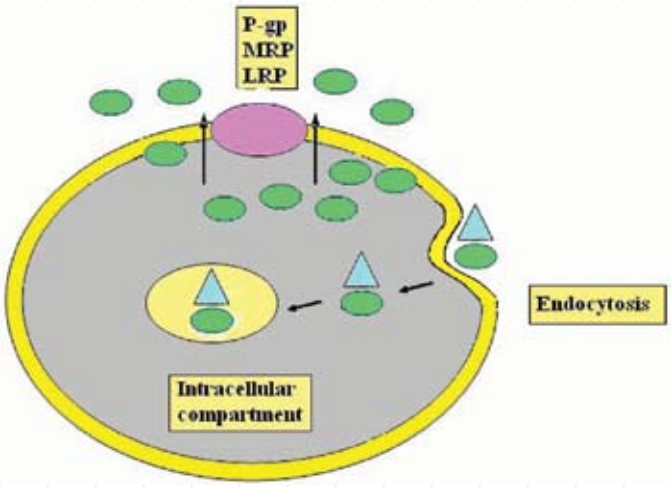


Figure 1. Nanomedicines overcome multidrug resistance by endocytosis–minimizing contact with P-gp at the inner leaflet of the cell membrane.

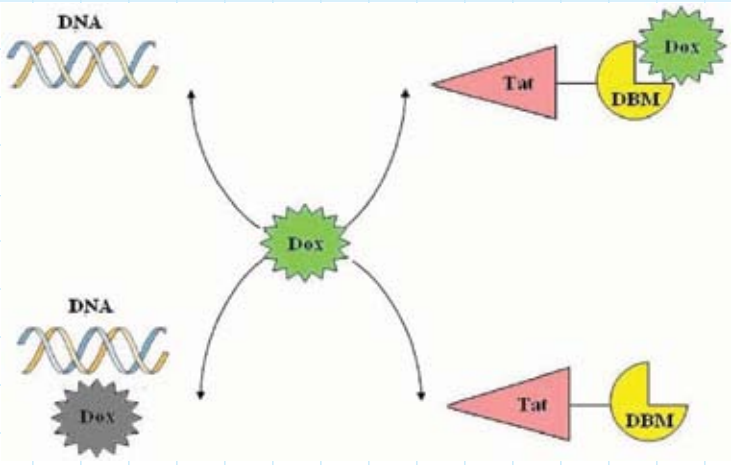


Figure 2. DNA displacement assay of doxorubicin (Dox) non-covalently bound to a peptide constructed from the cell-penetrating Tat and a drug-binding motif (DBM) associated with Dox. Dox fluorescence is quenched through intercalation of the drug between the base pairs of DNA (4), whereas Dox remains fluorescent when associated with the DBM-Tat peptide.

(Figure 3). DNA readily displaced any significant binding to the DBM or Tat peptides alone. However, the DBM-Tat hybrid peptide bound Dox sufficiently strongly to require at least fivefold molar excess of DNA before the majority of Dox bound was displaced by binding to DNA.

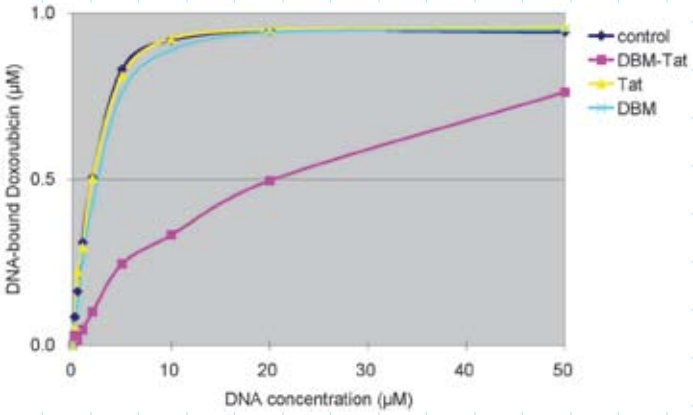


Figure 3. Displacement of Dox bound to DBM-Tat peptide by excess DNA. Dox (1 μM) was pretreated with 10 μM DBM-Tat, Tat, and DBM, respectively, for 1 hr at room temperature before the addition of DNA. Dox (1 μM) fluorescence and its quenching by DNA was assayed using a Perkin Elmer LS50B spectrofluorometer (Ex: 480 nm; Em: 590 nm).

Confocal microscopy was used to compare the cellular distribution of Dox uptake in the P-gp–mediated drug-resistant leukemia cell line KD30 (5). Free Dox was distributed throughout the cytoplasm in KD30 cells, appearing fluorescent in the cytosol, and quenched in the nucleus (Figure 4). Dox uptake via DBM-Tat resulted in a punctate perinuclear localization of fluorescence, suggestive of vesicular location in the cytoplasm, possibly including larger vesicles and Golgi bodies. The latter punctate pattern of Dox distribution was abolished by the endosomotropic agent chloroquine (CLQ), indicating that DBM-Tat may direct Dox through an endosomal pathway.

Conclusions

To the best of our knowledge, this is the first report of a hybrid peptide affecting non-covalent delivery of an MDR drug into resistant cells. The hybrid DBM-Tat peptide bound Dox with sufficient affinity to retain the drug until presented with a molar excess of DNA to displace the drug from the peptide. Dox bound to the hybrid peptide appeared to be redirected to perinuclear compartments in the cytoplasm, abolished by chloroquine and consistent with an endosomal route of uptake into the cells. DBM-Tat peptides could be a tool for the delivery of unmodified drugs into MDR cells and to provide a depot in vesicular compartments for sustained release within the cell.

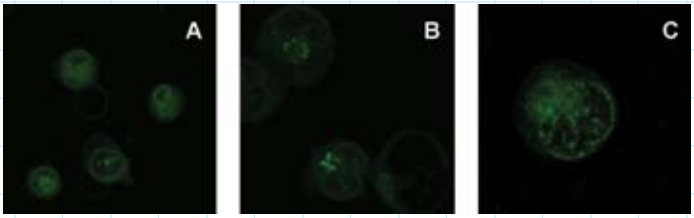


*Figure 4. Cellular disposition of Dox associated with DBM-Tat: KD30 cells treated with **A**, Dox (10 μM) alone; **B**, DBM-Tat (2 μM) + Dox (10 μM); or **C**, the same levels of DBM-Tat and Dox for cells pretreated with 100 μM chloroquine (CLQ).*

References

1. Leslie, EM, Deeley, RG, Cole, SPC. Multidrug resistance proteins: Role of P-glycoprotein, MRP1, MRP2, and BCRP (ABCG2) in tissue defense, Toxicol. Appl. Pharmacol. 204: 216-237 (2005).
2. Mazel, M, Clair, P, Rousselle, C, Vidal, P, Scherrmann, JM, Mathieu, D, Temsamani, J. Doxorubicin-peptide conjugates overcome multidrug resistance, Anti-Cancer Drugs 12:107-116 (2001).
3. Popkov, M, Lussier, I, Medvedkine, V, Esteve, PO, Alakhov, V, Mandeville, R. Multidrug-resistance drug-binding peptides generated by using a phage display library, Eur. J. Biochem. 251: 155-163 (1998).
4. Tarasiuk, J, Frezard, F, Garnier-Suillerot, A, Gattegno, L. Anthracycline incorporation in human lymphocytes: Kinetics of uptake and nuclear concentration, Biochim. Biophys. Acta 1013: 109-117 (1989).
5. Yague, E, Armesilla, AL, Harrison, G, Elliott, J, Sardini, A, Higgins, CF, Raguz, S. P-glycoprotein (MDR1) expression in leukemic cells is regulated at two distinct steps, mRNA stabilization and translational initiation, J. Biol. Chem. 278: 10344-10352 (2003).

SPOTLIGHT:

InterAg

By Michael J. Rathbone
Director of Research and General Manager
InterAg, Hamilton, New Zealand

InterAg began life in the 1980s as a division of the New Zealand-based plastics packaging company Carter Holt Harvey. In its early days, InterAg manufactured milking machine componentry, including injection-molded silicone gaskets. As InterAg evolved, the late Doug Millar initiated collaborations with animal scientist Bob Welsh with the aim of using silicone as an inert matrix to develop a product that addressed animal production needs. The outcome was InterAg's world-renowned injection-molded silicone/progesterone "CIDR" intravaginal insert for estrous synchronization of herds of sheep. A few years later, a collaboration with cattle physiologist Jock Macmillan resulted in a larger version of the sheep CIDR being developed for estrous synchronization of cattle. In 1995 InterAg became an independent business unit of Carter Holt Harvey and relocated to its current purpose-built manufacturing and analytical facilities at 558 Te Rapa Road, Hamilton, New Zealand. In 1997 it was purchased by its current owners, DEC International, Inc. A few years before the purchase, visionary CEO Bill Thompson initiated an ambitious program with the aim of gaining U.S. approval of the CIDR 1380 cattle insert (Figure 1). Dr. Michael J. Rathbone joined InterAg in 1995 to lead the re-engineering process for this product (1), develop in-house cGMP analytical and QC expertise, and guide InterAg through the U.S. approval process. Approval was granted in 2002, and InterAg became the first company in New Zealand to successfully register and

Figure 1. CIDR 1380 cattle insert.

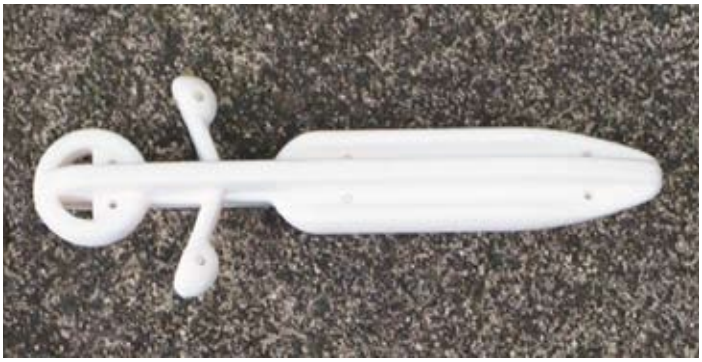


Figure 2. CIDR pig insert.

manufacture a U.S.-approved product. Success was facilitated through the generation of an immense amount of scientific knowledge behind the product and a focused, collaborative effort between the R&D and manufacturing divisions of the company. New insights into *in vitro* and *in vivo* drug release from silicone have been provided by InterAg over the years (1,2), and extensive numbers of publications have appeared in the literature evaluating the clinical efficacy of CIDR products (cited in reference 3).

Over the years the CIDR intravaginal products have had an extensive impact on the veterinary industry (4), providing not only an invaluable farm management tool, but also a research tool for animal scientists and veterinarians to further their knowledge on the physiology and endocrinology of the estrous cycle of cattle, sheep, and other species.

The silicone/progesterone technology was recently extended for use in pigs, under the direction of Dr. Rathbone in collaboration with Prof. Billy Day (University of Missouri, USA) (Figure 2). The challenging task to design and optimize the product was achieved through InterAg's historical experiences with the silicone CIDR product and generation of new knowledge that elucidated pig vaginal anatomy relevant to drug delivery (in-house reports). The pig CIDR product was registered on the New Zealand market in 2006.

In an attempt to maximize opportunities through its core competency of fabricating injection-molded veterinary products, InterAg developed the first biodegradable intravaginal insert for estrous control of cattle (5) (Figure 3). The product was registered on both the New Zealand and Australian markets in 2005.

Figure 3. Biodegradable PCL intravaginal insert.

Today, InterAg continues to grow and expand under the guidance and leadership of its General Manager and Director of Research, Dr. Michael J. Rathbone, who has established a first-class team of pharmaceutical and analytical scientists specializing in the innovation, research, development, and commercialization of controlled release veterinary drug delivery technologies. InterAg's business strategy is to leverage its own in-house expertise with collaborations with sister companies, universities, and research centers worldwide.

InterAg is currently researching several patent-protected pipeline products, including a novel rumen bolus. The flexible bolus technology allows for high drug loads, the potential for simultaneous delivery of multiple drug classes, the delivery of any drug type from water-soluble to lipid-soluble to insoluble compounds for durations of as little as 5 days to prolonged durations of up to 12 months. InterAg is currently undertaking the process of establishing a joint development agreement to align this innovation with a partner company to create a framework for meaningful collaboration.

References

1. Rathbone, MJ, Bunt, CR, Ogle, CR, Burggraaf, S, Ogle, C, Macmillan, KL, Burke, CR, Pickering, KL. Reengineering of a commercially available bovine intravaginal insert (CIDR insert) containing progesterone, J. Control. Release 85: 105-115 (2002).
2. Rathbone, MJ, Bunt, CR, Burggraaf, S, Burke, CR, Macmillan, KL. Optimization of a controlled release intravaginal drug delivery system containing progesterone for the control of estrus in cattle. Proc. Int. Symp. Control. Release Bioact. Mater. 25: 249-250 (1998).
3. Rathbone, MJ, Macmillan, KL, Jöchle, W, Boland, M, Inskeep, K. Controlled release products for the control of the estrous cycle in cattle, sheep, goats, deer, pigs and horses (invited review). Crit. Rev. Ther. Drug Carrier Syst. 15: 285-380 (1998).
4. Rathbone, MJ, Macmillan, KL. Application of controlled release science and technology: progesterone, Control. Release Soc. Newsl. 21: 8-9 (1998).
5. Rathbone, MJ, Bunt, CR, Ogle, CR, Burggraaf, S, Ogle, C, Macmillan, KL, Pickering, KL. Development of an injection molded poly (ε-caprolactone) intravaginal insert for the delivery of progesterone to cattle. J. Control. Release 85: 61-71 (2002). ■

Chapter News

Otago Hosts the Tri-nations of Solid State Research

In May 2007, the New Zealand Chapter of CRS (NZCRS) organised a 2-day workshop at the School of Pharmacy in Dunedin that saw leading experts in solid state pharmaceutical analysis share their knowledge with a group of 40 researchers and post-graduate students from Auckland, Waikato, and Otago Universities, as well as the pharmaceutical industry. The presenters of this workshop were Dr. Clare Strachan (chief research scientist in physical pharmacy, University of Helsinki), Prof. Anne Juppo (chair in industrial pharmacy, University of Helsinki), and Prof. Thomas Rades (chair in pharmaceutical science, University of Otago).

Left to right: Dr. Clare Strachan (Helsinki), Prof. Thomas Rades (Otago), and Prof. Anne Juppo (Helsinki).

The focus of the workshop was industrial dosage form design, as well as spectroscopic analysis of solid state characteristics of drugs and excipients. Each of the presenters gave high-quality, insightful presentations that showcased their depth of knowledge in the field. Prof. Juppo began the workshop by describing the pharmaceutical industry and its future challenges. Preformulation issues of solid dosage forms were then discussed, including excipient properties and techniques used to measure tablet characteristics. After lunch Prof. Juppo led an exciting interactive session during which participants were able to put in place some of the theories presented in the workshop. In small groups, participants worked through scenarios on the formulation of products, necessary in a variety of situations, such as when products come off a patient or when new drug molecules become available.

Prof. Juppo and Prof. Rades have had considerable experience working in both academia and industry, and they shared their insights on the role that pharmaceutical scientists can play in industry during a roundtable discussion with post-graduate students. This was a fantastic opportunity for the post-graduate students to discuss career options to further their development as formulation scientists. The NZCRS was pleased to be able to provide travel grants that enabled six students from outside the Otago area to attend the workshop.

On the second day of the workshop, Prof. Rades began with a discussion of the important issue of improving the solubility of poorly soluble drugs—a challenge that will predominate in the future of pharmaceutical formulation science. Integral to this topic, the formulation of drugs as amorphous solid dispersions was discussed.

Dr. Strachan presented a lecture on the fundamentals of spectroscopy for use in the analysis of pharmaceutical dosage forms, including a comparison of Raman, terahertz, and near infrared spectroscopy techniques. Analysis of spectral data using multivariate statistical analysis was also discussed in terms of how spectroscopy has an important role to play in process analytical technology (PAT).

This was the first time such a workshop has been held in New Zealand. The feedback from the workshop attendees was very positive, and everyone was able to enhance their knowledge in this exciting field of research.

Prof. Juppo and Dr. Strachan discuss scenarios with workshop participants (Left to right: Andy Lavrent, James Falconer, Anne Juppo, Vlad Syzov, Clare Strachan. and Julia Myschik). Photo by Manson Wright.

Profs. Juppo, Rades, and Dr. Strachan are all members of the Pharmaceutical Solid State Research Cluster (PSSRC). This newly formed group is an international network that links the six main research centers with expertise in pharmaceutical solid state research. The PSSRC provides a framework for collaboration, the exchange of post-graduate students, and the sharing of facilities between group members. For more information on the PSSRC, please visit www.pssrc.org.

We gratefully acknowledge the sponsors of this workshop: the New Zealand Local Chapter of the Controlled Release Society, the Formulation and Delivery of Bioactives Research Theme of the University of Otago, and the University of Helsinki, Finland. ■

United Kingdom & Ireland Controlled Release Society

By Dr. Leab Sek
Secretary, UKICRS

New UKICRS Chair
In October 2006, Prof. Yvonne Perrie (Aston University) took over from Prof. David Brayden as the chair of UKICRS. In her new role, Yvonne has continued to raise the committee profile and strengthened our position as an organisation representing and promoting the exchange of views between scientists from all disciplines who are interested in different aspects of controlled or advanced drug delivery.

UKICRS 13th Annual Symposium
Our 13th Annual Symposium on Drug Delivery Systems–In the Spotlight, held in January 2007 at the University of Nottingham, UK, was an great success, with approximately 100 delegates from both academia and industry. All credit for this excellent day must go to Assoc. Prof. Colin Melia (University of Nottingham), Dr. Snow Stolnik-Trenkic (University of Nottingham), Dr. Sarah Dexter (3M Healthcare), and Dr. Simon Banks (AstraZeneca).

Assoc. Prof. Colin Melia (School of Pharmacy, University of Nottingham) opened the symposium with a review of recent trends in oral extended release and gastro-intestinal (GI) targeted dosage forms. Matrix and coating remain the mainstay technologies for formulation development of extended release dosage forms, but recently there has been a surge of interest in GI targeting. The presentation by Prof. Juergen Siepmann (University of Lille, France) looked at the development and application of a mechanistic mathematical model to provide insight into the complex phenomenon of drug release from swelling matrix systems. A fundamental understanding of the interplay between factors known to influence drug release from these swelling matrices was used to define the structure of the model. Prof. Clive Washington (AstraZeneca, Macclesfield) provided an industry perspective on the development of colloidal medicines. Following a brief overview on the history of colloids, Prof. Washington described the main challenges faced by companies, including constraints on new technology, lengthy clinical trials, and demands by regulatory authorities. He admitted that colloids are poorly understood by formulation groups and regulators within the pharmaceutical industry due to their unpredictable behaviour, complex kinetics, and being non-amenable to the Arrhenius equation.

In a talk titled "Probing the Internal Structure of Surfactant-Based Delivery Vehicles," Prof. Jayne Lawrence (Kings College, London) gave a presentation on her group's work, which aims to increase the apparent solubility of poorly water-soluble drugs by solubilising them in micelles and microemulsions. Prof. Steve Brocchini (University of London) discussed the use of formulation strategies to aid progress in drug discovery. He noted that cost-affordable medicines are an unmet medical need, with many factors complicating successful development. In particular the formulation of medicines adds a lot of cost and complexity to the medicine. Fresh from a front page feature of the *Guardian*, Prof. Len Seymour (University of Oxford) discussed strategies for systemic delivery of therapeutic genes.

Emad Al-Muti and Prof. Yvonne Perrie at the UKICRS 13th Annual Symposium in 2007 at the University of Nottingham, UK

"The cure of all diseases" versus "wouldn't give it to my dog" are two of the common public opinions on gene therapy. Prof. Seymour acknowledged that gene therapy will only be a viable alternative in treating disease if the challenges in delivery are overcome. Closing the session, Prof. Kevin Shakesheff (University of Nottingham) discussed protein delivery from highly porous tissue-engineering scaffolds. He noted that the internal structure of a delivery system needs to be considered when used in regenerative medicines and that how such systems can enter and clear the body without destroying the cells also needs to be addressed.

UKICRS Newsletter
In July, our annual newsletter, *Newsletter 2007, Volume 12*, edited by Dr. Maura Kinahan (Pfizer Healthcare, Ireland) and Dr. Woei Ping Cheng (Robert Gordon University, UK), was released, providing another extremely interesting and informative edition. The *Newsletter* featured highly topical articles, including "From Solubilisation to Transporter Modulation to Controlled Release," by Dr. Ben Boyd and Assoc. Prof. Chris Porter (Monash University, Australia); "A Basic Guide to Physical Preformulation Studies," by Dr. Clare Armstrong (Patheon UK Ltd); "Simultaneous Sizing of Nanoparticles by Individually Visualizing and Separately Tracking their Brownian Motion within a Suspension," by Drs. Bob Carr, Andrew Malloy, and Patrick Hole (NanoSight Ltd, UK); "The Double-Barrelled Dissolution Equations," by Dr. Karl Malcolm (Queens University Belfast); "Supercritical Carbon Dioxide for Controlled Drug Delivery," by Drs. Owen Davies (Critical Pharmaceuticals Ltd, Nottingham), Martin Whitaker (Critical Pharmaceuticals Ltd, Nottingham), and Steve Howdle (University of Nottingham, UK); and "A Basic Guide to Photodynamic Therapy," by Drs. Paul McCarron, A. David Woolfson, and Ryan Donnelly. We were also privileged to feature an article on "An interview with the CRS President," Professor Randall Mrsny.

Chapter News continued on page 28

Chapter News continued from page 27

Within the global drug delivery community, we are continuing to develop links with other colleagues around the world, including the New Zealand and Indian Chapters. Prof. Perrie attended the 2007 Formulation and Drug Delivery Research Theme and New Zealand Local Chapter Conference earlier this year as the keynote speaker. Prof. Perrie gave a presentation on her work using cationic liposomes to enhance potency of tuberculosis sub-unit vaccines.

As in previous years, the UKICRS hosted a 1-day symposium at the British Pharmaceutical Conference (BPC) in Manchester in September 2007. Dr. Karl Malcolm, Prof. Jayne Lawrence, and Dr. Woei Ping Cheng arranged an excellent programme titled Nanotechnology in Drug Delivery and Medicine (further details are available on www.ukicrs.org and www.bpc2007.org).

For the remainder of the year, we are looking toward the 2008 Annual Symposium meeting and are already pulling together an interesting programme. Further details will be available on our website at www.ukicrs.org. ■

Erratum
CRS Newsletter
Volume 24, Number 2, 2007

In the Consumer and Diversified Products article "CeramiSphere: Micro-encapsulation and Controlled Release from Ceramic Particles" by Christophe Barbé, Kim Finnie, and Linggen Kong, the e-mail address provided as part of the authors' byline on page 17 should be cab@ansto.gov.au. The e-mail address johan.ubbink@rdls.nestle.com was included in error.

From Gastroretention to Pharmacogenomics—The Vet Sessions at Long Beach Covered It All

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

Those with an interest in patients of the four-legged variety had a diverse range of high-quality talks to choose from at the 2007 CRS Annual Meeting in Long Beach, California.

The Veterinary Mini-symposium was held on the first day of the conference, and we were treated to talks from international experts in the field of veterinary therapeutics and controlled release. The topic of the mini-symposium was Gastroretention – Animal vs. Human, and Kazuko Sagawa (Pfizer Global Research and Development, USA) opened the session by outlining the important differences in the structure and physiology of the gastrointestinal (GI) tract when comparing humans and veterinary species. As veterinary species are often used in preclinical studies for products intended for human use, it is important to consider species differences when interpreting pharmacokinetic data. For example, the length of the GI tract is shorter in dogs compared with humans, so the absorption of a drug may be underestimated when the data are extrapolated from dogs to humans. Clive Wilson (SIPBS, UK) presented a fascinating talk entitled "Accidental Gastroretention." Clive drew on clinical records from hospital emergency departments about unfortunate situations where items, such as batteries, mushrooms, and Barbie doll heads(!), had caused obstructions in the GI tract. Clive presented the case that these situations of accidental gastroretention can be used to the advantage of formulation scientists in learning about what makes good gastroretentive devices and the factors that predispose humans to bezoar formation, such as patients with cystic fibrosis who undergo thoracic surgery.

Keith Ellis (consultant, Australia) gave his characteristic lively presentation, the topic of which was "Gastro-retention – Large (Ruminant) Animals Versus Human." Extended gastroretention in humans over a time period of days is a goal in human medicine that has not yet been attained; however, dosage forms are available for cattle that can remain in the rumen for several years. The development of these long-lasting devices was driven by the need to treat entire herds of free-ranging animals with one administration. Keith reiterated the importance of understanding the GI physiology of the patient in question and made the point that the behaviour of the animal is also important. The retention of drug delivery devices in livestock is enhanced because these animals do not adopt a variety of different postures, as humans do (e.g., rolling over or sitting), which can affect the transit of material from the stomach.

Marilyn Martinez (FDA, Center for Veterinary Medicine, USA) directed our attention from oral dosage forms to the issues surrounding parenteral controlled release systems and the importance of achieving safety and efficacy. The *in vivo* factors that can alter drug release, and thus product performance, were discussed, and the important point was made that it is difficult to investigate the many interacting factors that occur *in vivo* using *in vitro* investigations.

The vet group continued the tradition of having an informal gathering, and we gratefully acknowledge the generous sponsorship of this event by Pfizer Animal Health. Terry Bowersock (Pfizer Animal Health, USA) was the speaker at this get together, and he presented an excellent global perspective on the choice of administration of pharmaceuticals for veterinary applications and the needs of the future.

The veterinary track at Long Beach was centred around the theme of Emerging Roles of Alternative Delivery in Veterinary Medicine. The invited speaker for this session was Katrina Mealey from the College of Veterinary Medicine, Washing State University, USA, who gave a fascinating talk (including videos) on pharmacogenetics of drug receptors in companion animals and why some breeds of dog are more sensitive to the effects of drugs than others. The catch phrase "white feet don't treat" was coined to remind veterinarians that collie dogs are susceptible to toxicity from ivermectins. Katrina discussed their work on identifying the MDR1 polymorphism that causes changes in the expression of p-glycoprotein in the blood brain barrier.

Massimo Faustini (Department of Veterinary Science and Technology for Food Safety, University of Milan, Italy) was the next speaker in the session. He discussed his research on the artificial insemination of sows with semen encapsulated in controlled release capsules composed of barium alginate. The aim of this research was to improve the preservation of spermatozoa when frozen and was the first large-scale trial of its kind, with 3,493 sows included in the study!

Ian Tucker (School of Pharmacy, University of Otago, New Zealand) gave an excellent talk on the effect of polyethylene glycol on release of vitamin B_{12} from ethylene-vinyl acetate copolymer films. The application of this work is to develop an implant that will deliver B_{12} and improve the growth of lambs grazed on pastures that are cobalt deficient.

From the Vet Group continued on page 30

From the Vet Group continued from page 29

Helena Florindo (School of Pharmacy, University of Lisbon, Portugal) presented a series of comprehensive studies investigating the treatment of strangles disease in horses caused by *Streptococcus equi*. Polymeric nanoparticles (PCL and PLA) were investigated as antigen delivery systems. Intranasal administration of antigen encapsulated in PCL nanoparticles increased the IgG titre for 12 weeks in a mouse model.

Raid Alany (School of Pharmacy, University of Auckland, New Zealand) ended the session with a talk on rheological and micro-structural characteristics of *in-situ* gelling systems for ocular drug delivery in the treatment of pinkeye infections in livestock. The polymers investigated included carrageenan, alginate, and chitosan. All demonstrated good spreading characteristics, which would enhance residence time in the eye, and the polymers were found to be non-toxic. ■

CRS Education Committee Young Scientist Workshops at the 2007 CRS Annual Meeting

By Roderick B. Walker
Rhodes University
Grahamstown, Republic of South Africa

The 2007 Young Scientists Education Workshop organized under the auspices of the CRS Education Committee, and the fourth to be held at an annual meeting of the Controlled Release Society (CRS), was once again a resounding success. These workshops, which are designed to introduce young scientists (defined as anyone under the age of 40 or anyone who has entered the area of controlled release within the last five years), are the brainchild of Dr. Michael Rathbone, former chair of the Education Committee.

The 2007 program was organized by Farid Dorkoosh, assisted by Mike Rathbone, Rod Walker, Bridgitte Skalsky, Brian Carlin, and Teresa Virgallito, and generously sponsored by Intervet. The workshop was attended by approximately 120 delegates over one and a half days. Whilst the format of the workshops was different from previous years in that there was a full-day and a half-day workshop, it provided an excellent opportunity for young scientists to listen to, and meet, experts in the field of controlled release of bioactive consumer and diversified products.

The full-day workshop focused on the application of the basics of pharmaceutical sciences in drug delivery and discussed the considerations and challenges for developing sustained release formulations from academic and industrial perspectives.

In the morning session, Juergen Siepmann gave an excellent overview of the concepts of diffusion and its importance in understanding dosage form performance. Thomas Rades eloquently discussed issues relating to solubility and provided "food for thought" with respect to the impact of amorphous and crystalline structures on solubility. Raid Alany followed with a superb introduction to aspects of flow, rheology, and viscosity in relation to sustained release formulation. Outstanding overviews on topics relating to polymeric surfactant chemistry, colloid chemistry, and preparation, characterization, and pharmaceutical applications of hydrogels were delivered by Glen Kwon, Sven Frokjaer, and Wim Hennink, respectively.

The afternoon session involved presentations relating to the formulation and processing challenges associated with the manufacture of sustained release systems and was chaired by Brigitte Skalsky (Degussa Pharma) and Brian Carlin (FMC BioPolymer). The session commenced with a succinct overview of controlled release tablet and pellet technologies by Rod Walker and provided the foundation for an interesting and well-structured session. Brian Carlin presented two excellent reviews of research relating to the use of celluloses in conventional sustained release multiparticulate and matrix systems. Nasser Nyamweya identified the issues relating to the formulation and processing of multiparticulate sustained release systems using methacrylate polymers, and Brigitte Skalsky used several innovative animations to reveal aspects of methacrylate polymer use in functional film coatings as they pertain to processes, parameters, and formulations. The final presentation of the day, by Vishal Gupta, was an excellent summary of solubility and the physicochemical properties of an active pharmaceutical ingredient in relation to biopharmaceutics in the development of oral controlled release delivery systems.

The half-day workshop allowed the Consumer and Diversified Products section of the CRS to introduce young scientists to the use of controlled release technologies in the areas of personal care, flavor and fragrance, and industrial applications. The young scientists were also exposed to
IP availability and searching and fluid bed technology. Presenters in this workshop were Teresa Virgallito, Ronald Versic, Nava Dayan, Claudio Ortiz, Anil Gaonkar, Douglas Dale, and Charles Frey.

In addition to the Young Scientists Education Workshop, two Get Up! Get Educated! sessions again formed part of the program for 2007. In the first of these two highly educational and informative sessions, Raimer Loebenberg gave an entertaining introduction to aspects of "*In-vitro/In-vivo* Correlation." The second presentation was delivered by Brian Crist, who elucidated for the audience the basics of *in vitro* dissolution testing. Both sessions were well received and attended by over 100 delegates.

From the Education Committee continued on page 32

From the Education Committee continued from page 31

At the Awards Ceremony and Banquet the past chair of the CRS Education Committee, Mike Rathbone, was announced as the recipient of Distinguished Service Award for his contribution to the CRS. Well done Mike.

The CRS Education Committee has worked hard this year to maintain current and introduce new initiatives. The focus on young controlled release scientists continues to be important, and a mentoring programme has been set up on a trial basis. This initiative pairs a young scientist with an expert and is the focus of the industry section of the Education Committee. In addition, several education articles have been published in the *CRS Newsletter* under the CReators banner, and there are several education articles that have been commissioned on controlled release education around the world and from speakers in the Young Scientist Workshops. A new and exciting initiative that is being developed is the delivery of webinars; the first of these is likely to take place before the end of 2007. The committee intends to hold four of these prior to the next CRS Annual Meeting. In addition, the Young Scientist Workshops for 2008 will include a session on aspects of challenges associated with veterinary controlled release technologies. Watch this space for updated information.

For more information on the CRS Education Committee, its activities, and if you are interested in serving on the committee, please contact Farid Dorkoosh at f.d@nobleceuticals.com. ■

CRS Education Committee Plans Workshop in Conjunction with the 2007 AAPS Annual Meeting

Be sure to join the CRS Education Committee's Industrial Section and sponsors, Northern Lipids, Inc., and Pfizer, Inc., November 9–10, 2007, for its Development and Regulatory Challenges for Controlled Release Formulations Workshop. The workshop will be held in conjunction with the 2007 AAPS Annual Meeting in San Diego, California, and will offer a full two days of expert speakers discussing the topics you want to hear more about. CRS members receive the AAPS member discounted rate when registering for the workshop, so take advantage of this CRS member benefit and register today!

As an attendee, you will gain an understanding of the development challenges surrounding controlled release formulations utilizing mature and new, evolving technologies, discuss regulatory challenges encountered in the development of a controlled release drug formulation and how to overcome them, share fundamental science and experiences that will be of value to you when dealing with various controlled release technologies, and meet with other scientists and regulatory authorities in an informal atmosphere. This workshop will increase your knowledge of a variety of controlled release technologies that may not be found in your literature searches and help you acquire knowledge to assist you in the design of your own pharmaceutical products. There will be two panel discussions on Friday and Saturday that will further open the dialog between the presenters and audience.

Workshop Chairs Ron Ortiz, Mike Rathbone, Dody Reimer, and Avi Thombre are pleased to bring CRS and AAPS together to offer this outstanding two-day workshop. To whet your appetite, below are a few of the speakers and the topics they will discuss:

The Road to the Six Month ELIGARD® Product – Rick Norton, QLT Inc., U.S.A.

Development Consideration for Innovative Passive Transdermal Drug Delivery – David Kanios, Juan Mantell, and Christopher McDaniel, Noven Pharmaceuticals, Inc., U.S.A.

Development and Regulatory Challenges for Pulmonary Products – Andy Clark, Nektar Therapeutics, U.S.A.

Development and Regulatory Challenges in Osmotic Technology – Suneel Gupta, ALZA Corporation, U.S.A.

Developing Multiparticulate-Based Drug Products: Process Understanding and Control – Scott Herbig, Pfizer, U.S.A.

Scientific and Regulatory Challenges in Controlled Release Formulations – Krishnan Tirunellai, Health Canada, Canada

MF59 Is a Safe and Potent Vaccine Adjuvant for Human Use – Manmohan Singh, Novartis Vaccines, U

Nanotechnology: Opportunities in Drug Delivery – W. Mark Saltzman, Yale University, U.S.A.

Drug Nanosuspensions: From PK Modification to Disease Targeting – Barrett Rabinow, Baxter HealthCare, U.S.A.

The Science and Regulatory Perspectives of Controlled Release Products with Emerging Technologies – Mansoor Khan, FDA, U.S.A.

Registration is open. Visit www.aapspharmaceutica.com/meetings/annualmeet/am07/ to sign up now. ■

What's on Board

CRS Board Members—Adding New Faces and Saying Good-bye

With the passing of the gavel at the Aquarium of the Pacific in Long Beach, California, three CRS members took their new offices on the Board of Directors. Diane Burgess (University of Connecticut) took her place as Vice President, Ijeoma Uchegbu (University of London) stepped into the Scientific Secretary position, and Elka Touitou (Hebrew University of Jerusalem) settled in as the newest Member-at-Large.

At the Awards Ceremony, CRS was pleased to honor retiring Board members Vladimir Torchilin (Northeastern University), Martyn C. Davies (University of Nottingham, and Clive Wilson (University of Strathclyde). Vladimir served on the CRS Board as Vice President, President-Elect, President, and Immediate Past President from 2004 to 2007. Martyn held the position of Scientific Secretary from 2001 to 2007. Clive served a three-year Member-at-Large term beginning in 2005 in Miami and ending this year in Long Beach.

The Board of Scientific Advisors welcomed new members at their BSA meeting on Sunday, July 7: Joke Bouwstra (Leiden/Amsterdam Center for Drug Research), Marcus Brewster (Johnson & Johnson), Claudia Leopold (University of Hamburg), Mariko Morishita (Hoshi University), and Patrick Sinko (Rutgers University).

Having fulfilled their three-year terms on the BSA, Todd Becker (Genencor International), Terry Bowersock (Pfizer Animal Health), Karsten Cremer (Pharma Concepts), Paul Gellert (AstraZeneca), and Elka Touitou (Hebrew University of Jerusalem) were all recognized during the Long Beach Awards Ceremony. Their contributions to the CRS are appreciated.

2007–2008 CRS Board of Directors
President – Susan Cady
Intervet, Inc., U.S.A.
President-Elect – Lisbeth Illum
IDentity, U.K.
Vice President – Diane Burgess
University of Connecticut, U.S.A.
Immediate Past President – Randall Mrsny
University of Bath, U.K. and Trinity BioSystems, Inc., U.S.A.
Treasurer – Arthur Tipton
Brookwood Pharmaceuticals, Inc., U.S.A.
Scientific Secretary – Ijeoma Uchegbu
University of London, U.K.
Member-at-Large – Elka Touitou
Hebrew University of Jerusalem, Israel
Member-at-Large – Ian Tucker
University of Otago, New Zealand

2007–2008 Board of Scientific Advisors
Joke Bouwstra
David Brayden
Marcus Brewster
Igor Gonda
Kazunori Kataoka
Claudia Leopold
Betina Martinez
Mariko Morishita
Ralph Niven
Thomas Rades
Sevda Senel
Patrick Sinko
Ron Smith
Rod Walker ■

Welcome New Members

Abhiruchi Agarwal
Rihab Ahmed
Sungsook Ahn
Kristy M. Ainslie
Dorcas Ajao
Jun Akimoto
Parvin Akther
Laman Alani
Tom Alfredson
Mohammed Habib Ali
Leonard B. Allison
Christine Andersen
Gandhi Ankur
Steven Ansell
Mary F. D. Avila
Eri Ayano
Sungmin Bae
Manuela Banciu
Stephen M. Berge
Bret Berner
Laurence Besse
Jeroen Bezemer
Krishna Hari Bhandari
Worawan Boonyo
Amol Borade
Binoy Bordoloi
Corinne Bright
Calvin T. Broman
Colleen Brophy
Beth A.-S. Brown
Tarq Bunch
Jonathan J. Burbaum
Horacio A. Cabral
Daniel Callahan
Timothy Callahan
Fabio Campanile
Yilmaz Capan
Jeffrey Carbeck
Denise Catini
Fabio Caviggioli
Valérie Centis
Christine Anne Cezar
Sudhir Chakravarthi
Ariel Chan
Barbara P. Chan
Cheuk Ming Chan
Hee Chul Chang
Hsin-I. Chang
Yuan-Chia Chang
Manoj Shrawan Charde
Ying Chau
David Chen
Mei-Chin Chen
Yongming Chen
Kyle Chenet
Kuei-Chen Chiang
Shook-Fong Chin
Ya-Ling Chiu
Han-Gon Choi
Ki Young Choi
Suna Choi
Young Jun Choi
Yahya E. Choonara
David Christian
Hee Sun Chung
Joo Eun Chung
Young Lim Chung
Suchada Chutimaworapan
James Henry Paul Collins
Sally-Ann Cryan
Ramesh Dandu
Kiem H. Dang
Ayelet David
Tapas K. De
Albert De Bruin
Menno De Jong
Marc De Mul
Kashappa Goud Desai
Elisabeth Deschamps
Ninad Deshpanday
Michael DesJardin
Volga Devabhaktuni
Venkat R. Devadasu
Harikrishna Devalapally
Gopinath Devaraj
Aylvin Dias
Mario A. Diaz de la Rosa
Tanver Doganay
Martin Joseph Donovan
Philippe J. M. Dor
Timothy A. Dotson
Anitha Rajesh Dudhani
Joel Eary
Christine Eckberg
Geraldine Elliott
Desai Esha
Jim Fang
Massimo Faustini
Christian B. Felder
Marcel Fens
Kathleen Fischer
Carlos Fleet
Eric A. Forssen
Sarah Pretz Foster
Deborah Fox
Miller N. Freitas
Beth Fryksdale
Jack Furuno
Srinivas Ganta
Jun Gao
Paolo Gatti
Sanjay Gayakwad
Robert Gianello
Bianca Glaessl
Gunnar Gloeckl
David Goldman
Victoria Gong
Jonathan Goole
Amit Goren
Tarun Goswami
Takanori Goto
Dorte X. Gram
Tais Gratieri
Stephanie E. A. Gratton
Mark A. Gray
Xinyi Gu
Junjie Guan
Karen Guhr
Robert Edmon Guisinger
Emilio Gutierrez
Stefan Haas
Elran Haber
Annina Hafner
Mark Hall
Ehab Hamed
Justin S. Hanes
Joerg Hanisch
Samara Hantman
Wei Hua Hao
Lester I. Harrison
Azadeh Sadat Hashemi Doulabi
Teemu Heikkila
James C. Heitz
Pernille Hemmingsen
Mindi Hertzog
Peter G. Hessell
Kaoru Hida
Santosh Hire
Praveen S. Hiremath
Juliane Hombach
Ondrej Hovorka
Dai Phu Huynh
Jungyeon Hwang
Marc Antoniu Ilies
Jum Imai
Naoki Ishii
Kevin B. Ita
Takashi Izumi
Satishkumar Jain
Byeongmoon Jeong
Rachaneekorn Jevprasesphant
Ge Jiang
ChengHao Jin
Joseph P. Jiuliano
Jung Chul Joo
Tommy Julianto
Mira Jung
Suk Hyun Jung
Yoshinori Kakizawa
Daniel Takashi Kamei
Hideko Kanazawa
Vibhu Kanchan
Hyewon Kang
Ji-Youn Kang
Ling-Ling Kang
Mitsunobu R. Kano
Yoshiko Katori
Richard Kaye
Saito Kazuhiro
Jina Y. Kazzaz
Cornelia M. Keck
Michael Kennedy
Nick Kennedy
Edward Kerslake
Sing Tze Kho
Hanmoe Ki
JaYoung Kim
Jiseok Kim
Ji-Young Kim
Ju Mi Kim
Junoh Kim
Kyung-Hee Kim
Stephanie Heekyong Kim
Sungwon Kim
Tae Hyung Kim
You-Kyoung Kim
Robert Patrick Kinsey
Jason J. Klein
Sandra Klein
Alexander L. Klibanov
Robbert J. Kok
Rohit Kolhatkar
Ja-Seong Koo
Julius Nartey Korley
Rebecca L. Koval
Thomas Krol
Achim H. Krotz
Harish P. M. Kumar
Motoichi Kurisawa
HeeSeung Kwon
Young Min Kwon
Isabelle L. Lagadic
Hoyin Lai
Liselotte Langkjaer
Bert Lao
Susan W. Larsen
Erin E. Leary Swan
Segolene Leclercq
Deok Keun Lee
Jaein Lee
Jun-Young Lee
Myung Hak Lee
Sang Won Lee
Seul Ki Lee
Susan Shu-Hsun Lee
Stephen Levine
Jennifer M. L'Hote-Gaston
Dongxun Li
Guohua Li
Luk Chiu Li
Michael Li
Nai-Hong Li
Vincent H. Li
Xinhua Li
Xinsong Li
Xue Li
Yufu Li
Yuping Li
Likan Liang
Jason Lichti
Chia-En Lin
Chuen-Chang Lin
Frank C. Lintz
Hongwei Liu
Hui Liu
Xin-Ming Liu
Ya-Chin Lo
Nathan Lockwood
Robert J. Lollini
Kenneth R. Lomartire
Norbert Loos
Luciana B. Lopes
Patricia Santos Lopes
Won Seok Lyoo
Xinghang Ma
Garth MacDonald
Julia Maier
Narasimhan Mani
George Mattheolabakis
Laura Maurer
Warren Trethowen McBurney
Ryan McElroy
Shayna L. McGill
Natalie Medlicott
Elsie Melsopp
Kathrin Meyer-Bohm
Remi Meyrueix
Fwu-Long Mi
Kelly Miller
Mi Hong Min
Shahrzad Missaghi
Richard Mitchell
Girish Mittal
Haruna Miyauch
Patrick Mohr
Naomi Moldavski
Richard A. Moore
Behzad D. Mottahed
Naweed Muhammad
Gour Mukherji
Seong-Joo Na
Takehisa Nakajima
Daisuke Nakamura
Barrett Nehilla
Pushp Raj Nepal
Madhuri Newa
Erik Nestor Newman
Khanh Minh Nguyen
Thanh Nguyen
Tri-Hung Nguyen
Giovanni Nisato
Mare Nishiura
Hagen Nitzsche
Marina Dénise Nordberg
David Michael Oakley
Stephen O'Brien
Adrienne Oda
Ryoko Ogura
Eun Ju Oh
Keun Sang Oh
Sabrina Oliveira
Fernanda Onofre
Praneet Opanasopit
Marion Oudshoorn
John Ouyang
Deborah Jean Paetznick
Shrikant N. Pagay
Rebecca Noelle Palumbo
Dong-Min Park, Sr.
In Park
Seong-Bae Park
Sun Woo Park
Young-Jin Park
Siddhesh D. Patil
James A. Patindol
Laura Patrick
Jeisa Mari Pelet-Giraud
Chih-Kang Peng
Gabrielle Pilcer
Johan Pluyter
Patrick D. Pohlhaus
Ketul C. Popat
Clive A. Prestidge
Amy Preszler Prince
Reema Puri
Yongxing Qiu
Sabrina C. Rainey
Suriyakala Ramalingam
Maxime Ranger
Amit Rawat
Gabriele Reich
Samuel Reinhold
Sigrun Reinwald
Sarah Lynette Reiver
Cristianne J. F. Rijcken
Victoria Rogers
Theerasak Rojanarata
Edith C. Rojas
Celestino Ronchi
Cornelia Rose
Ginger Rothrock
Mads Christian Sabra
Usawadee Sakulkhu
Rania Salama
Imran Y. Saleem
Susnata Samanta
Tomohiko Sano
Sigal Saphier-Sharabany
Aparna Reddy Sarasam
Shuji Sato
Yuko Sato
Amarpreet S. Sawhney
Dieter Scherer
Peggy Schlupp
Robert Schmitt
Larry Wayne Schneider
Sylvia Schreiber
Karen Schultz
Gun Seomoon
Abu Serajuddin
Jaymin C. Shah
Yosi Shamay
Suresh L. Shenoy
Praveen Sher
Hyoung-Goo Shin
Park Shin Jung IV
Tomohiro Shirosaki
Adam J. Shuhendler
Duangratana Shuwisitkul
Srujana Siddoju
Kellie Silver
Pierre Simard
Pavla Simerska
Spomenka Simovic
Ankur Singh
Sarabjit Singh
Summer L. Sivas
Igor N. Skidan
Alan M. Smith
Saeil Sohn
Yoen Ju Son
Andreas Sophocleous
Frank L. Sorgi
Sutthilug Sotthivirat
John Stankus
Brigitte Stark
Scott Staton
Peter Steelman
Sebastian C. J. Steiniger
Pnina Strasbourger
Sangwon Suh
Bo-Kyung Sun
Victor Sun
Suvimol Surassmo
Richard K. Suzuki
Yusuke Suzuki
David Sylvester
Pompilia I. Szabo
Scott J. Szedlock
Seiji Takae
Angel Tan
Grace Tan
Benjamin Tang
Rupei Tang, Sr.
Shih-Yi Tang
Yutaka Tanoue
Paul Tardi
Tony Taylor
Zeynep Teksin
Ildikó Terebesi
Nartaya Thirawong
Delacy J. Thomas
Torben Thomsen
Koji Tokutomi
Takao Tomono
Istvan Toth
Olga Trubetskoy
Chi-Chun Tsai
Shimoboji Tsuyoshi
Scott A. Uhland
Hiroyuki Umejima
Takeo Urakami
Saroj Vangani
Eric H. Van Ness
Lilian Van Vlerken
Deepali Vartak
Kumar Vedantham
Yvonne Verburgt
Michael L. Vieira
George A. Voyiatzis
W. Douglas Walkling
Scott Walsh
Jiansheng Wan
Chau-Hui Wang
Chung-Yih Wang
Daniel N. Wang
Hong Wang
Jianzhuo Wang
Jong-Jing Wang
Mao Wang
Wayne Wang
Xuli Wang
Alice W. Ward
Wayne P. Weiner
Xin Weng
Kathryn Whitehead
Alexandre Williams
Kyungjae Won
Dennis Wong
Sharon Y. Wong
Dae Gyun Woo
Paul M. Wortel
Ming Wu
Tzu-Hui Wu
Siegfried Wurster
Fred Xi
Loh Xian Jun
Bibo Xu
Peng Xu
Rongzuo Xu
Guang Yan
Yimin Yan
Jinghua Yang
Sara Yazdi
Jay Ye
Feng-Lin Yen
Yun Yeon Hee
Richard C. Yocum
Mi-Kyong Yoo
Hye Jeong Yoon
Hang Yu
Shu-huei Yu
Abdel-azim Zaghloul
Samuel Zalipsky
Ayse Zamboglu
Guodong Zhang
Hongwei Zhang
Junhua Zhang
Li Zhang
Ningrong Zhang
Ying Zhang
Tao Zheng
Zhaohua Zheng

Patent Watch

By Jamileh Lakkis, Ph.D.

Searching the consumer and diversified products patent literature for the first six months of 2007 revealed a significant increase in the number of inventions for oral care compositions and devices, especially chewing gums. This surge is due not only to the traditional function of these products as breath fresheners, but also to the current trend in utilizing these formats as delivery vehicles for a variety of actives ranging from flavors and nutraceuticals to nicotine and other drug actives. This review will summarize notable patents (filed and granted) pertaining to oral care and nutraceuticals, as well as flavors and fragrances.

Vehicles for Oral Care with Magnolia Bark Extract (GIC Innovations, U.S.A.) WO 2007/064519 A1

A natural oral hygiene composition based on magnolia bark extract (MBE) for inhibiting plaque-causing bacteria and oral biofilm is claimed. A synergistic effect is also disclosed for combinations of MBE and surface active agents such as sodium dodecyl sulfate (SDS), presumably due to increased solubility of the MBE and enhanced diffusion through the biofilm. *In vitro* effectiveness of the composition was demonstrated using three typical sublingual plaque bacteria associated with malodor and compared with cyclohexidine (positive control) and sterile water (negative control), as well as other natural ingredients with known anti-plaque properties, such as green tea. The rsults showed that the performance of MBE, although less effective than chlorhexidine, was superior to that of green tea, especially in inhibiting the growth of *S. mutans* and biofilm formation. MBE potential applications include chewing gum, breath film, mouth washes, and other oral care products.

Medicated Chewing Gum Delivery System for Nicotine (S. R. Cherukuri, J. M. Pinney, J. E. Henningfield, A. Sasan, E. J. Cone, S. Shiffman, J. Gitchell, C. D. Malvestutto) US 2007/0014887 A1

A chewing gum composition for improved nicotine delivery mechanism and reducing nicotine cravings is disclosed. The composition is claimed to be superior to commercial nicotine delivery devices in many respects, mainly in its controlled pH and unique texture. The composition is designed to maintain alkaline pH levels (8–9) throughout a chewing period of up to 30 minutes, increasing release and overall effectiveness of nicotine absorption. The soft texture is also claimed to be beneficial for overcoming the dependence of nicotine release on conscious chewing by the user. The unique biphasic release profile was composed of a first phase during which chewing for ≈10 minutes resulted in up to 60% of the nicotine being released, providing rapid pharmacological onset and slower release thereafter to maintain stable levels of the active in the subjects' blood.

Cleaning and/or Polishing Compositions and Methods for Use Thereof (Colgate-Palmolive, U.S.A.) WO 2007/076396

An oral care composition with cleaning and polishing attributes, a challenging combination in oral care preparations, is disclosed. Also disclosed is a device for controlling and sequential release of abrasive particles having different physicochemical properties. The patented composition consists of 1) an outer surface with a first abrasive material (particle size 5–15 μm) for initial low cleaning action, and 2) a film containing a second abrasive material (smaller particle size 0.5–5 μm) for higher cleaning power. Disintegration of at least a portion of the film via saliva exposes the second abrasive material embedded in the film. Controlling the physical orientation of the polishing particles by aligning their configuration with respect to the surface is claimed to be advantageous in providing the film with an effective planar orientation, thus increasing its surface area and enhancing the particles efficiency and cleaning action.

Enzyme Containing Oral Composition Having Enhanced Stability (Colgate-Palmolive, U.S.A.) US 2007/7220404 B2

This patent discloses an oral care composition comprising cetyl pyridinum chloride, stable proteases, and cellulase enzyme inhibitors. While cetyl pyridinum chloride and proteases play a positive role in cleaning the gums and oral cavity, cellulases, residual components in protease preparations, are implicated in plaque formation. The latter is a result of the ability of cellulase to degrade cellulose, a common thickener in oral care preparations, into smaller carbohydrate species. Using an *in vitro* cleaning model, the inventors claim that compared with a commercial oral rinse containing only cetyl pyridinum chloride, the inventive rinse with inactivated cellulase resulted in a significant reduction in total and interproximal plaque by 67% and displayed effectiveness in cleaning in interproximal regions, demonstrating a "floss-type" action.

Cleaning Perception Oral Care Products (Whitehill Oral Technologies, U.S.A.) US 2007/0107747 A1

A novel approach for coating dental devices such as flosses and tooth picks with flavor "top notes" to provide instant sensory

Patent Watch continued on page 36

Patent Watch continued from page 35

impact is disclosed. Traditionally, it has been very challenging to apply volatile flavors to dental flosses and similar devices due to the high temperatures involved in the injection molding manufacturing process. Attempts to post-coat these devices often have resulted in an unsightly appearance that distracts from consumers' acceptance of such products. The method claimed in this patent involves first coating the injection-molded floss with a mixture of non-volatile flavor and a film-forming material, such as celluloses (CMC, HPMC), followed by assembly of the device into a final package that contains a volatile flavor reservoir in the form of an adsorbent paper or polyvinyl acetate polymer impregnated with the "top notes" and tightly sealing the container. Upon equilibrium, the volatile flavors migrate from the reservoir to adsorb onto the coated device, resulting in a dental floss with intense flavor notes, thus providing the user with a perception of cleanliness.

Medicated Gum Stick for Treatment in Anti-inflammatory Conditions and Prophylaxis Against NSAID Gastropathy (Medical Futures, Canada) WO 2007/000038 A1

A chewing gum containing pain-relief NSAID and an H_2 antagonist for treating inflammation conditions while alleviating the NSAID side effects, including GI toxicity and stomach lining damage, is claimed. The patented composition is constructed of a 3-compartment assembly, where the NSAID is separated from the H_2 antagonist via a slab of flavored antacid such as calcium carbonate. Claimed advantages of the compartmentalization include separating the low pH NSAID so it is not in direct contact with the H_2 antagonist that is prone to degradation under such conditions. The composition is claimed to provide significant improvement in the active's bioavailability, a result of its absorption via the buccal mucosa.

Oral Composition and Method for Stress Reduction Associated with Smoking Cessation (Wrigley's, U.S.A.) WO 2007/041035 A2

This patent describes a flavor composition for alleviating side effects associated with the consumption of nicotine chewing gums and other smoke cessation treatments. The composition is based on vanilla and peppermint flavors that are claimed to be effective in reducing stress in smokers undergoing smoking abstinence. The peppermint and vanilla flavors are claimed to provide these benefits by decreasing saliva cortisol in test subjects in a 3-day trial following smoke cessation. Using visual analog scale (VAS) values, the degree of urge to smoke (subjective) was reduced significantly in both groups, although the effect was more pronounced in the vanilla flavor consuming group.

Food Composition Comprising Glucosamine (Nestec, Switzerland) US 2007/0141018 A1

This patent discloses a method for extracting glucosamine from root plants in high yields. Glucosamine is an important amino-monosaccharide that plays an essential role in maintaining healthy skin and is often incorporated into cosmetic preparations for this purpose. The uniqueness of this process lies in the finding that glucosamine is formed by partial Maillard reaction and not by degradation pathways from glucosoaminoglycan or other polymers, as is the case with current commercially available products. The patented process involves harvesting plant roots from chicory, carrot, or Jerusalem artichoke, cutting and drying at relatively high temperatures, followed by aqueous extraction and purification. The inventors suggest that the glucoaminoglycan formed is a result of the interaction between the released fructose and amino acids via first step Maillard reaction, i.e., sugar condensation and Amadori rearrangement without formation of browning species.

Compositions and Methods for the Sustained Release of β-Alanine (Natural Alternatives International, U.S.A.) WO 2007/073398 A2

This patent describes a composition for sustaining the release of β-alanine, providing a method for the safe and effective increase of carnosine biosynthesis in muscle. β-Alanine is critical for maintaining muscles and is generated by the body or can be obtained from dietary sources. Adequate intake of β-alanine provides a means to attenuate metabolic acidosis and delay the onset of fatigue during anaerobic exercise via production of carnosine. Due to its instability, however, dietary intake of β-alanine requires frequent dosing, which often results in paraesthesia and an associated abnormal burning sensation. Sustained release of β-alanine, claimed in this invention, can attenuate the rise in blood plasma concentration and reduce metabolic acidosis and muscle fatigue during anaerobic activity.

Compositions for Regulating Intestinal Disorders and Methods for Use Thereof (Perque, U.S.A.) WO 2007/056432 A2

A delivery system in the form of tablets or powder for alleviating and/or regulating GIT disorders is claimed. The system is composed of therapeutic levels of prebiotic material, selenium source, proanthocyanins, and phosphatides. In addition to enriching the diet with fiber, the composition claims benefits such as converting lipid hydroperoxides to less harmful compounds via selenium and providing anti-inflammatory agents via proanthocyanins.

Black Tea Extract for Prevention of Disease (Rutgers, U.S.A.) US 2007/7238376 B2

Compositions and methods for prevention and treatment of cancer are disclosed. The composition is based on black tea extracts that include a mixture of theaflavin-3-gallate and theaflavin-3′-gallate denoted as TF-2. The patented composition is claimed to provide unique benefits, mainly inhibition of the expression of the *Cox-2* gene associated with inflammation reactions and carcinogenesis at the mRNA and protein levels. TF-2 is also claimed to reduce the proliferation of W138 and W138VA cells, as well as growth of Caco-2 cells in culture. The composition is suggested as a suitable component for food and dietary supplements in various formats such as drink mixes, capsules, confections, and others.

Extracts of Orange Peel for Prevention and Treatment of Cancer (Rutgers, U.S.A.) US 2007/7201928 B1

Compositions for inhibiting tumor cell growth and preventing or treating cancer based on orange peel extract, mainly the 4′,5,6,7,8-pentamethoxyflavone and 3′,4′,5,6,7,8-hexamethoxyflavone components are disclosed. When tested in an *in vivo* model for colon cancer, the patented orange peel extract and nordihydroxyguaiaretic acid (NDGA) showed 48 and 48% inhibition in the number of aberrant crypt foci (ACF) per colon, respectively. Similarly, the ratio of AC/ACF was inhibited by 51 and 34% for NDGA and the patented orange peel extract, respectively. The patent also highlighted the synergistic effect of the extract's main two components, tangeretin and nobeletin, on inhibiting cell growth; no such effect was found for the individual components.

Microparticulate System for the Oral Administration of Biologically Active Substances (Universita Degli Studi di Milano, Italy) WO 2007/072535 A2

This patent discloses a preparation of flavonoid microcapsules and their controlled delivery in animal health applications. The gastro-resistant preparation is claimed to provide slow GIT transit and enhanced bioavailability of flavonoids, mainly quercetin and rutin, substances that are effective for stimulating the animal's immune system. Using different combinations of polymethylacrylates, acrylates, alginates, and polaxamer, release of the flavonoids was significantly reduced at pH 1.0 (<15% in simulated gastric juice), while at pH 7.5 quercetin release was >75%.

Bioavailability Enhancing Activity of *Carum carvi* Extracts and Fractions Thereof (Council of Scientific and Industrial Research, U.S.A.) US 2007/0020347 A1

This patent claims use of extracts of *Carum carvi*, a bioenhancer, either alone or in combination with piperine or *Zinzeber officionale* extract, to improve the bioavailability of a wide array of drugs, especially antibiotics and antivirals. Following the Ayurvedic approach, this composition is claimed to enhance drug absorption and bioavailability and inhibiting or reducing the rate of biotransformation in the liver and intestines. Examples of significant bioactivity enhancement were provided for the drug rifampicin.

Composition of *Hoodia gordonii* and Pinolenic Acid Derivatives (R. G. Udell) US 2007/0104805 A1

A method and composition for enhancing weight loss are disclosed. The composition is based on the well-documented benefits of the African plant hoodia, which has received scientific and press attention over the last few years. Hoodia can help in appetite suppression by promoting the feeling of satiation, presumably due to the role of its steroidal glycoside, which is endowed with cholecystokinins-like activity that "fools" the brain into thinking the stomach is full. The patent claims that a most beneficial composition includes, in addition to hoodia, pinolenic acid extracted from pine nuts. This fatty acid is promoted for its desirable effects, such as maintaining a high muscle to fat ratio, a result of increasing insulin sensitivity so fat and glucose can bypass cell membranes and avoid additional deposits in fatty tissues. The claimed composition can be prepared in the form of capsules, drink mixes, lozenges, and other formats.

Benzoquinones of Enhanced Bioavailability (S. Olsen, J. A. Doney, C. S. Shores) US 2007/0026072 A1

A method for enhancing bioavailability of CoQ_{10} and other benzoquinones is disclosed. CoQ_{10} is a lipid-soluble benzoquinone produced by anaerobic organisms or is chemically synthesized. It is a powerful antioxidant with membrane-stabilizing effects. It is also recommended as a dietary supplement for regulating metabolism and for its effectiveness in alleviating symptoms of Alzheimer's, Parkinson's, and cardiac diseases. One of the main challenges in using CoQ_{10} in food and nutraceutical preparations is their crystallinity and associated limited bioavailability. This patent claims that encapsulating benzoquinones such as CoQ_{10} with polymers such as CMC or PVP can promote the active's bioavailability and help control its release in various food and beverage systems.

Food Comprising Silicon (Psimedica Ltd, U.K.) WO 2007/012847 A1

This patent discloses processes for preparing elemental silicon and for loading it with active components for their controlled release in food systems. The choice of the silicon species (amorphous, single-, or poly-crystalline) depends on the active's physicochemical properties, mainly particle size and specific application. The active can be chemically bound or deposited onto the silicon particle surface or incorporated into its pore. The high porosity of silicon species claimed in this invention makes them ideal for burst aroma delivery, in particular for beverage applications where the loaded silicon can float on the surface of the container to produce high sensory impact in the beverage headspace. Etched silicon (HF-etched) is claimed to possess additional advantages for loading hydrophobic actives and flavors.

Nanoemulsion Composition and Methods of Use Thereof (Texas A&M University, U.S.A.) US 2007/0085058 A1

A polycationic complexation formulation for treatment of hypercholesterolemia and bone mineral loss is claimed. The nanoemulsion formulation comprises a protein complex having an e-transfer bridge between interfaces of the nanoemulsion and a sulfated polysaccharide and an electron transfer mediator and protein stabilizer. Nanoemulsions made with caprine phosphopeptide (CPP), calcium, and eggplant extract, known for its effect in enhancing calcium bioavailability and phospholipids solubility, are claimed to possess powerful cholesterol-reducing abilities (67.3%).

Sustained Release Creatine Formulations (CR Technologies LLP, U.K.) GB 2429915 A

Compositions for controlled release of bioactives such as enhanced creatine retention and transport are claimed. Despite

Patent Watch continued on page 38

Patent Watch continued from page 37

the ability of the human body to synthesize creatine in the liver and pancreas, additional dietary sources are often required for the regulation and homeostasis of skeletal muscle energy, protein synthesis, and hypertrophy of muscle fibers during training. The claimed formulations do not rely on insulin-mediated transport nor do they require ingesting higher levels of the active. The compositions covered by this invention encompass encapsulating creatine with cellulose acetate phthalate (CAP) to control its delivery at a constant rate (i.e., at V_{max} ±30% of muscle creatine transporters) so the body tissues can retain suitable levels of the active in the plasma, thus enhancing creatine muscle uptake.

Process for Encapsulation of Edible Oil Products with Whey Protein and Encapsulated Edible Oil Products (Cambridge Applied Polymers, U.K.) WO 2007/012847 A1

Formulation and processes for encapsulating ω-3 fatty acids is disclosed. The inventive formulation is based on emulsifying oil droplets and further entrapping them in a whey protein-carboxymethyl cellulose (CMC) gel matrix. While whey protein acts as an emulsifier and gelling agent, CMC, especially under acidic conditions, serves as a matrix stabilizer, presumably due to its involvement in H-bonding with whey protein components. A two-step process is described whereby the whey protein-oil preparation is gelled via acid treatment, dried, and milled to form a half-product. The resulting powder is resuspended in CMC-acid medium to form a secondary gel matrix that can be dried and ground to appropriate particle size for further topical application on food products such as breakfast cereals.

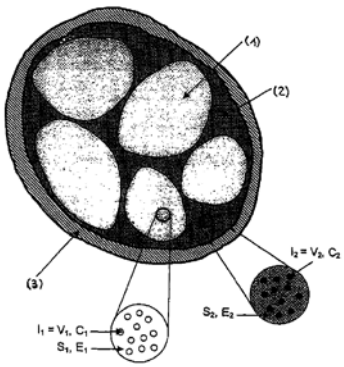
Prebiotic Oligosaccharides via Alternansucrase Acceptor Reaction (Board of Trustees Western Illinois University, U.S.A.) US 2007/7182954 B1

An enzymatic treatment for generating oligosaccharides with superior prebiotic properties is disclosed. The process is based on treating sugars with glucansucrases, a class of extracellular enzymes secreted by bacteria (*Lactobacillus*, *Streptococous*, and others) that are classified as glucan synthesizers as well as sucrases. Glucansucrases act by transferring D-glucosyl units from sucrose to D-glucose polymers with concomitant release of fructose, an important acceptor reaction of glucansucrases. These enzymes also have the ability to catalyze acceptor reactions with various sugars, such as maltoses and gentibioses, and can form two or more linkage types with a single acceptor. Prebiotics prepared using the alternansucrase treatment are claimed to be more selective than the best performing commercial prebiotic ingredients (Neosugar™) in enhancing *Bifidobacterium* activity but do not support the growth of pathogenic anaerobes such as *Clostridium perfringes*.

Compositions and Methods Based on Synergies Between Capsicum Extracts and Tea Catechins for Prevention and Treatment of Cancer (Purdue Research Foundation, U.S.A.) US 2007/7192612 B2

This patent claims a therapeutic dietary supplement composition containing catechins, such as epigallocatechin gallate (EGCG) or epicatechin gallate (ECG), and capsicum extracts for the prevention and treatment of cancer. This potent composition is claimed to deliver its therapeutic effect by inhibiting the activity of a cancer-specific protein, an isoform of NADH-oxidase (tNOX), with minimal adverse effect on normal healthy cells that express the isoform cNOX but lack the tNOX. The co-administration of EGCG with capsicum extract is suggested to be essential for avoiding the recurrence of cancer cells and for preserving normal cell growth.

Fragrance Compositions (Givaudan, Switzerland) US 2007/7166567 B2



This patent describes a unique controlled release system for delivering a combination of volatile and non-volatile fragrance components. The system comprises a two-compartment assembly where discrete core particles, i.e., inner compartment, are enclosed in an outer matrix (see Figure). The highly volatile or soluble components (loss factor, F2 < 10^2 Pa ppm) are entrapped in the discrete core particles to provide greater protection and delayed release while the outer compartment entraps the less volatile and/or less water-soluble components (loss factor > 10^2 Pa ppm) of the fragrance material. The discrete particles are first prepared by spray-drying a fragrance emulsion or dispersion; the dried particles are further placed in a conical fluidized bed granulator and are coated with another emulsion of carbohydrates or polyvinyl alcohol with fragrance components of low volatility to form the outer compartment.

Flavor Precursor Composition and Method for Releasing the Flavor Component (Ajinomoto, Japan) US 2007/7011860 B1

A method and composition for controlling the release of volatile mercapto-group containing flavor components, such as methanethiol or propanethiol, essential for freshly brewed coffee and meat flavors is disclosed. Due to their low threshold and high volatility, the release of these species can be very challenging. The patented method involves reacting the volatile mercapto compounds with their non-volatile mercapto-containing counterparts in the presence of a catalyst such as $CuCl_2$ and the formation of a stable disulfide compound. Cleavage of the S-S bond is triggered in the presence of reducing agents and/or heat, thus releasing the labile volatile mercapto-group component.

Method for Measuring the Leaching of Encapsulated Material into Application Media (IFF, U.S.A.) US 2007/0154378 A1

This patent describes an analytical method for separating actives from capsule material using dialysis filtration, i.e., principle of chemical equilibrium. The method is also claimed to overcome drawbacks involved in routine solvent extraction methods (e.g., long time, reduced efficiency, extensive calibration, need for media concentration, etc.). The system is in essence a dialysis membrane with selective permeability for active molecules but is impermeable to the capsule material. The filtered media are claimed to be suitable for direct injection to GC or HPLC. One major benefit claimed by the inventors is the suitability and accuracy of this method for measuring concentration of very low vapor pressure flavors as well as preparations with high surfactant levels (≈5%) and the potential for conducting relative binding-affinity measurements of flavors/actives in various media. ■

CRS Headquarters & Staff

3340 Pilot Knob Road
St. Paul, MN 55121 U.S.A.
Telephone: +1.651.454.7250
Facsimile: +1.651.454.0766
www.controlledreleasesociety.org

Steven C. Nelson, *Executive Vice President*
+1.651.994.3832
snelson@scisoc.org

Barbara Mock, *Director of Finance*
+1.651.994.3829
bmock@scisoc.org

Amy Hope, *Vice President of Operations*
+1.651.994.3827
ahope@scisoc.org

Jody Grider, *Director of CRS Operations*
+1.651.994.3862
jgrider@scisoc.org

Lisa Anderson, *Administrative Coordinator*
+1.651.994.3809
landerson@scisoc.org

Jordana Anker, *Technical Editor*
+1.651.994.3866
janker@scisoc.org

Leah Barna, *Meeting Planner*
+1.612.813.0363
lbarna@scisoc.org

Susan Casey, *Meeting Coordinator*
+1.651.994.3846
scasey@scisoc.org

Beth Elliott, *Marketing Associate*
+1.651.994.3847
belliott@scisoc.org

Cheryl Sundquist, *Member Relations Specialist*
+1.651.994.3801
csundquist@scisoc.org

Ronda Thompson, *Education Manager & Sponsorship Sales*
+1.651.994.3836
rthompson@scisoc.org

Debby Woodard, *Exhibits & Advertising Sales*
+1.651.994.3817
dwoodard@scisoc.org

InTheNews

Compiled by Steven Giannos
Industrial Editor

Phosphagenics Limited Announces Positive Phase 1b Transdermal Insulin Clinical Trial Results

August 8, 2007 – Phosphagenics Limited (ASX: POH, AIM: PSG, OTCQX: PPGNY) has announced the successful completion of its Phase 1b transdermal insulin trial. The positive results of this trial demonstrated that its TPM technology delivered insulin into the bloodstream in a non-invasive manner without causing adverse reactions. The Phase 1b clinical trial, conducted at the Royal Adelaide Hospital by CMAX, an independent clinical research organization, assessed the efficacy and safety of two improved TPM/Insulin formulations in 45 volunteers. Blood glucose, endogenous insulin and C-peptide levels were measured to assess efficacy.

Key items:

1) TPM/Insulin, applied topically, delivered insulin through the skin and into the bloodstream for up to 8 hr.
2) TPM/Insulin significantly lowered blood glucose, endogenous insulin, and C-peptide levels.
3) TPM/Insulin did not produce any adverse reactions.
4) Phase 2 trial to commence as soon as possible following ethics approval.
5) TPM carrier platform has again demonstrated the ability to deliver large molecules (e.g., proteins) through the skin in humans.

Similar responses to TPM/Insulin were achieved in the 2006 Phase 1a trial, but as a consequence of the research to improve the technology, the Phase 1b results showed a more sustained effect and greater statistical significance. Dr. Esra Ogru, executive vice president of research and development at Phosphagenics, said "The Phase 1b trial showed that our TPM/Insulin formulation safely penetrated through the human skin and delivered insulin into the blood stream over a sustained period of time, without causing adverse reactions. The improved formulation demonstrated that we have made significant progress in our goal of delivering insulin through the skin in a non-invasive manner."

Phosphagenics intends to continue clinical development of its transdermal insulin. Preparations are underway for a Phase 2 trial to be conducted by CMAX at the Royal Adelaide Hospital under the guidance and supervision of Assoc. Prof. William Hsu of the Joslin Diabetes Centre (Harvard Medical School) and Dr. Sepehr Shakib (director, Department of Clinical Pharmacology Royal Adelaide Hospital). They are also currently in the process of compiling an investigational new drug package that would allow the company to continue its Phase 2 clinical trial program in the United States after the completion of the Australian trials.

MicroDose Announces Positive Results from the QDose Inhaled Insulin Glucose Clamp Study

PR Newswire: August 6, 2007, MONMOUTH JUNCTION, N.J. – MicroDose Technologies, Inc., a privately held drug delivery and specialty pharmaceuticals company, has announced top line results from a glucose clamp study of the QDose inhaled insulin product. MicroDose, through its joint venture with Vectura Group plc, QDose Limited, has developed a highly efficient, rapid-acting, insulin inhaler, based on MicroDose's proprietary electronic inhaler technology and Vectura's dry powder insulin formulation. The QDose inhaled insulin product offers dose titration capability over a broad range of dose strengths in a single inhalation. The inhaler also provides active dose feedback to the patient in an easy-to-use, pocket-sized device.

The study employed the widely used and validated glucose clamp technique, and results demonstrated that

1) The inhaled insulin formulation was safe and effective.
2) Peak levels of insulin activity were achieved more quickly following the inhaled insulin than those from the subcutaneous insulin injection.
3) Relative bioavailability of inhaled insulin was approximately 18% during the 3-hr period following dosing; higher than the published values for the currently marketed inhalation product.
4) Administration of the same total dose of inhaled insulin from either a single blister or two "half-strength" blisters led to equivalent activity; an advantage over the currently marketed inhalation product.

The study was a randomized, crossover, open-label glucose clamp study designed to confirm the high relative bioavailability of the QDose insulin formulation previously observed and to demonstrate the product's dose titration capability. The results confirmed the faster onset of action seen with the QDose inhaled formulation compared with subcutaneous insulin. The relative bioavailability observed in this study compares favorably with available information on competitor inhaled insulin programs. The study was conducted in the United States at the Profil Institute for Clinical Research Inc. in San Diego, California, with 14 healthy male volunteers, using a glucose clamp technique. For further information please visit MicroDose's website at www.microdose-tech.com.

Encore Therapeutics Inc. Reports Additional Proof of Concept Results on Its Extended Release Ropivacaine Injectable Gel for Postoperative Pain Management

Business Wire: August 2, 2007, CARLSBAD, Calif. – Encore Therapeutics Inc. (ETI) has reported on two pre-clinical studies demonstrating that its intradermal extended release ropivacaine gel formulation (ETI-211) has a markedly improved safety and pharmacokinetic (PK) profile compared with the currently marketed ropivacaine solution formulation. No apparent toxicity was shown with the ETI-211 gel at the highest ropivacaine dose used (2,054 mg/kg), in marked contrast to the 54 mg/kg lethal dose for the

solution formulation. The PK study showed that ETI-211 produced a greatly extended release profile lasting for 6 days and a 5- to10-fold reduction in C_{max} compared with the currently marketed solution formulation. The controlled and sustained PK profile is highly desirable since ETI-211 is designed to maintain the drug at the local site of administration. The PK result is consistent with the previously reported sustained pain-relief efficacy data.

ETI-211 is a proprietary non-liposomal phospholipid gel (PG) formulation that incorporates the drug in a single-phase depot system. The gel is capable of delivering the drug for 3–7 days with low burst potential and is made with existing injectable phospholipids and other components that have been used in previous FDA-approved drug products. Previously reported results have shown that ETI 211 outperformed another liposomal anesthetic depot formulation in terms of duration of action in pre-clinical models. For more information, contact Encore Therapeutics Inc., Paul J. Marangos at +1.619.787.4083 or visit www.encoretherapeutics.com.

Illuminating the Future of Drug Delivery

August 2, 2007 – Irish researchers have developed a technique that could be used to deliver controlled amounts of drugs to diseased tissues while minimizing side effects simply by shining light on the target. Researchers from Queens University in Belfast, Ireland, have developed a technique that uses light to turn a pro-drug into an active pharmaceutical via a photochemical reaction and precisely control the timing and amount of drug formed. The research, published as an early view article in the *Journal of the American Chemical Society* (JACS) shows how pro-drug molecules containing a carboxylic acid group can be turned into ester-containing drugs simply by shining a light source on them.

While using light in various photodynamic therapies has met with considerable success for cancer therapies and even MRSA antibiotics, the ability to precisely control drug doses to a target area has remained elusive. This new drug release process begins when light falls on the compounds and lasts only as long as the light continues to shine.

According to Dr. Colin McCoy, lead author of the study, the paper is the first step toward a new type of system that makes use of our ability to precisely control light to deliver accurate amounts of drugs. One of the key advantages of the approach is that drugs could be delivered at the site where they are needed without needing to expose the entire body to the drugs, dramatically reducing the potential for adverse side effects to occur. He stresses that the research is still in the *in vitro* development stage and that they are currently looking for ways to develop the technology for clinical use. "We're currently thinking that rather than letting the drugs circulate the whole way round the body, we could incorporate them into medical polymers that could be placed at the site of diseased tissue," said Dr. McCoy.

The researchers are currently looking at expanding the technique to classes of drug molecule other than the ester-containing systems studied in the paper. The systems would produce drugs whenever they are exposed to light, so the final manufacturing steps would need to be conducted in dark areas with the systems being packaged in silver foil-type containers.

J&J to Cut up to 4,820 Jobs on Drug Woes

AP: July 31, 2007, TRENTON, N.J. – Johnson & Johnson announced it will reduce its global work force by up to 4%, or up to 4,820 jobs, to cut costs due to slumping sales of heart stents and its No. 2 drug, plus looming patent expirations. The healthcare giant, which employs about 120,500 people in 57 countries, said the restructuring—its largest ever—will bring pretax charges of $550 million to $750 million later this year, as well as other unspecified steps in addition to job cuts.

Three of the company's top drugs, with combined sales of about $8.5 billion, are vulnerable. J&J's top seller, the anti-psychotic drug Risperdal, loses patent protection next June; Topamax, for epilepsy and other disorders, does so in March 2009. During the second quarter, sales of J&J's key anemia drug Procrit, formerly the company's best-selling drug, slid 6% to $758 million amid worries over safety concerns and possible limits on federal reimbursement for all drugs that stimulate red blood cell formation. It had sales of $3.2 billion in 2006.

Since last fall, reports have been raising safety questions about drug-coated stents, tiny mesh scaffolds that prop open heart arteries and slowly release a drug to keep them from reclogging. Among other things, research has shown most patients with drug-coated stents face a higher risk of heart attacks and death than patients with bare-metal stents.

In another statement, Johnson & Johnson-owned Alza Corp. said it will close its Mountain View, California, office and eliminate about 600 jobs. About 200 employees working in Mountain View will be transferred to La Jolla, California, and other Johnson & Johnson offices.

Under the restructuring, Johnson & Johnson will cut 3–4% of the work force, consolidate some pharmaceutical operations, and further integrate its Cordis businesses to better serve heart doctors. J&J also will streamline functions such as human resources, information technology, purchasing, and finance.

Menopausal Spray Flashing Hot

July 31, 2007 – Menopausal women in the United States will soon be free of hot flashes when a mist sprayed on the forearm becomes available next year. EvaMist (estradiol MDTS), developed by Australian drug delivery company Acrux and marketed in the United States by KV Pharmaceutical Company, has received marketing approval in the United States from the U.S. Food and Drug Administration (FDA).

The spray-on treatment for vasomotor symptoms associated with menopause has been estimated to be worth $125 million in peak annual sales when it enters the lucrative U.S. market, anticipated to be in the first quarter of next year. The spray delivers estradiol, a naturally occurring estrogen, through the skin of, preferably, the inner forearm via a fine mist in a handheld applicator. The estradiol is then absorbed into the blood stream on a sustained basis over 24 hr, providing a once-a-day dosing regime.

The fast-drying U.S. patented formulation is made up of the drug, a penetration-enhancing substance derived from a sunscreen extract, and a volatile solvent.

In the News continued on page 42

In the News continued from page 41

The effect after the spray dries in 45 sec would be somewhat like an "invisible patch," but no mark or residue would be left on the skin, Acrux Chief Executive and Managing Director Dr. Richard Treagus told US-PharmaTechnologist.com. Clinical studies show that rubbing or washing does not remove or impact the dosing of the spray, he said.

The spray device is based on a disposable unit with an accurate dose-delivery mechanism; a doctor may prescribe one, two, or three sprays depending on symptoms. This would be the first product available in the U.S. market for Acrux and the first transdermal spray approved by the FDA.

KV acquired the U.S. rights to EvaMist from Acrux's licensee VIVUS in March of this year for a cash consideration of $150 million plus further amounts of $30 million if EvaMist achieves annual net sales of $200 million. KV also assumed VIVUS' obligation to pay royalties to Acrux. Acrux has retained rights for all other areas outside the United States and is in discussion with several partners to exploit those markets. Earlier this year, Acrux licensed the spray technology to biopharmaceutical company Organon for a spray-on contraceptive. The drug delivery company is also developing a spray testosterone formulation to treat decreased libido in women and fentanyl to treat chronic pain.

Dermatrends Announces Positive Developments in Moisturization and Exfoliation Study

PR Newswire: July 26, 2007, MINNEAPOLIS, Minn. – Dermatrends, Inc., a drug delivery and skin sciences company, announced today that it has demonstrated positive results in a human study to evaluate its proprietary hydroxide releasing agent (HRA) technology on human skin for moisturization and exfoliation (removal of dead skin cells). The study validated that Dermatrends' HRA technology can be used to improve the efficacy of commonly used moisturizing and exfoliating agents. This milestone study opens the door for Dermatrends to move beyond drug delivery and to participate in the dynamic cosmetic personal skincare market.

The study, conducted by Hill Top Research, used a sample coded (identity blinded) method to compare the effect of Dermatrends formulations, as well as two commercial branded products. Comparisons were made for both Dermatrends formulations and the control commercial products against initial baseline values and an untreated negative control site. Study subjects ranged in age from 21 to 65 years. Dermatrends' formulation showed a statistically significant change from the baseline for both moisturization and exfoliation. Exfoliation is a central purpose of anti-aging cosmetic products.

Dermatrends is a privately-held drug delivery and skin sciences company based in Minneapolis, Minnesota. The company is currently actively developing its partnerships and other relationships in the global pharmaceutical and cosmetic industries to commercially introduce its technology. Additional information is available on the company's website at www.dermatrends.com.

Carrington and Brookwood Pharmaceuticals Extend GelSite® Drug Delivery Technology Development

PR Newswire-FirstCall: July 20, 2007, IRVING, Tex. – Carrington Laboratories, Inc. (Nasdaq: CARN) has announced that its subsidiary, DelSite Biotechnologies, Inc., extended a joint development agreement with Brookwood Pharmaceuticals, Inc. The goal of this effort is to continue an expanded evaluation of GelSite®, a DelSite patented drug-delivery technology, as a matrix for injectable applications and for selected classes of drugs. This extension is built on the promising results and evaluations conducted by the joint technical team in the past year.

GelSite® polymer is a high molecular weight anionic polysaccharide that exhibits distinct chemical and functional properties proprietary to the company. It is a naturally derived, biocompatible, resorbable biopolymer and is produced under cGMP with high purity at a kilogram scale. This technology has the potential to protect and deliver peptides and proteins effectively while reducing the frequency of drug administration. Fewer injections will improve patient compliance, safety, and efficacy. Injectable, controlled release applications for peptides and proteins are in the multibillion-dollar drug delivery market. Under this new extended joint development program, the evaluation of GelSite® technology will continue to be managed by a team of experts from Brookwood Pharmaceuticals and DelSite.

Antares Announces Worldwide Development and License Agreement with Jazz Pharmaceuticals

Business Wire via NewsEdge Corporation: July 19, 2007, EWING, N.J. – Antares Pharma, Inc. (AMEX: AIS) announced that it has signed a worldwide product development and license agreement with Jazz Pharmaceuticals (NASDAQ: JAZZ). Signing this agreement demonstrates the successful completion of a feasibility agreement that was initiated between Antares and Jazz Pharmaceuticals in December 2005. The product candidate underlying this agreement is being developed to treat a significant CNS disorder and is based on Antares' proprietary ATD™ (advanced transdermal delivery) system. Approved products from the same class of compounds represented worldwide sales of over $2 billion in 2006 and are projected to achieve sales of at least $3.1 billion in 2010.

Jack E. Stover, president & CEO of Antares Pharma, said "Moving forward with Jazz Pharmaceuticals is another significant validation of the quality, versatility and commercial potential of our ATD™ delivery system. We are extremely pleased with our progress in a key therapeutic area of CNS and believe it will help patients in an important and meaningful way."

Noven to Acquire JDS Pharmaceuticals, Expanding Business Model and Broadening Product Pipeline

NewsRx.com: July 19, 2007 – Noven Pharmaceuticals, Inc. (NASDAQ: NOVN) announced that it has agreed to acquire JDS Pharmaceuticals, LLC for approximately $125 million cash at closing plus the assumption of approximately $10

million in net liabilities. Based in New York, JDS is a privately held specialty pharmaceutical company that currently markets two branded prescription psychiatry products through a targeted sales force and is advancing a significant pipeline of high-potential products in psychiatry and women's health.

TransPharma Medical Announces Positive Results of Phase I Clinical Trials for Transdermal Delivery of hPTH (1-34) for Osteoporosis Treatment

July 9, 2007, LOD, Israel – TransPharma Medical Ltd., a specialty pharmaceutical company focused on the development and commercialization of drug products utilizing a proprietary active transdermal drug delivery technology, has announced promising results of its Phase I clinical trials that demonstrate the safety and pharmacokinetic profile of its ViaDerm-hPTH (1-34) product for the treatment of osteoporosis. A 7-day, repeated dose application, parallel group study was conducted on 48 healthy, elderly, post-menopausal women. The study was designed to evaluate the safety and tolerability of ascending multiple doses of hPTH (1-34) patches and to compare the pharmacokinetic profiles of the transdermally delivered doses of hPTH (1-34) with that of FORTEO® administered subcutaneously.

Transdermal hPTH (1-34) was delivered using TransPharma's fully integrated product, which is comprised of a proprietary pocket-sized device and 1-cm^2 dry hPTH (1-34) patch with demonstrated room-temperature stability. Once-daily transdermal delivery of all doses tested in this trial demonstrated a safety profile similar to the one observed in the FORTEO® subcutaneous injection. All safety parameters (including calcium and phosphorous) of the different transdermal doses were within the normal range. Furthermore, all ViaDerm-hPTH (1-34) doses were very well tolerated by participants. Pharmacokinetic profiles of hPTH (1-34) on the first and seventh day were similar, showing no accumulation of hPTH (1-34) levels and no deterioration in hPTH (1-34) systemic levels. These findings demonstrate the ViaDerm-hPTH (1-34) product's ability to provide reproducible drug levels that result in excellent inter- and intra-participant variability. Transdermally delivered hPTH (1-34) of all doses showed desirable peak profiles with relative bioavailability of approximately 40%. This bioavailability is among the highest reported bioavailability of alternative drug delivery routes to subcutaneous administration.

"We are very excited by the results of our Phase I studies. The promising findings are further validation that the ViaDerm-hPTH (1-34) product can provide a viable alternative administration route for hPTH (1-34) for women suffering from osteoporosis, which would alleviate the pain and inconvenience associated with their current treatment, thereby increasing compliance," said Dr. Daphna Heffetz, CEO of TransPharma Medical Ltd. "Strongly encouraged by the results of our series of Phase I studies, which included a total of 66 post-menopausal healthy women volunteers, we plan to initiate a Phase II study of the ViaDerm-hPTH (1-34) product, bringing this potential product to an advanced clinical stage before seeking a partner to take it to market," Dr. Heffetz added.

TransPharma's ViaDerm drug delivery system incorporates a handheld electronic control unit combined with a drug patch. The system provides a cost-effective, easy-to-use, self-administered solution that enables the safe, reproducible, and accurate delivery of a wide variety of product candidates, including hydrophilic small molecules, peptides, and proteins.

Exelon® Patch, the First and Only Skin Patch for the Treatment of Alzheimer's Disease, Receives First Worldwide Approval in United States

PR Newswire-FirstCall: July 9, 2007, EAST HANOVER, N.J. – The Exelon® patch (rivastigmine transdermal system) has received its first worldwide approval in the United States as an innovative way to deliver an effective medicine for patients with mild to moderate Alzheimer's disease through a skin patch instead of an oral capsule. The once-daily skin patch offers a novel approach to treating mild to moderate Alzheimer's disease, providing smooth and continuous drug delivery over 24 hr. This new therapy is the first and only transdermal treatment for this degenerative condition that affects millions of people in the United States. The Exelon® patch offers effective treatment based on placebo-controlled clinical trial results that show significant benefits to patients in terms of their memory and overall functioning.

Key points:

1) Similar efficacy to highest doses of Exelon® capsules, with significant improvement in memory and overall functioning compared with placebo.
2) Exelon® patch preferred by caregivers in a study because it helps manage patient care and gives visual reassurance that medication has been administered.
3) Exelon® patch minimizes gastrointestinal side effects seen with oral form of drug.

The Exelon® patch maintains steady drug levels in the bloodstream, improving tolerability and allowing a higher proportion of patients to receive therapeutic doses compared with the capsule form of the medication. It is applied to the back, chest, or upper arm and provides smooth and continuous delivery of medication through the skin over 24 hr. Gastrointestinal side effects are commonly seen with this class of drugs, called cholinesterase inhibitors. The recommended Exelon® patch dose greatly reduces these side effects, with three times fewer reports of nausea and vomiting than with the capsule form of the drug.

The Exelon® patch is expected to be available in U.S. pharmacies soon. The medication was submitted for review in the European Union in late 2006. The patch was designed with compliance in mind and was preferred to capsules by 70% of caregivers as a method of drug delivery according to clinical study data, because it helped them follow the treatment schedule, interfered less with their daily life, and was easier to use overall than the oral medication.

The approval of the Exelon® patch is based on results from the international IDEAL (Investigation of transDermal Exelon® in ALzheimer's disease) clinical trial, involving nearly 1,200 patients with mild to moderate Alzheimer's disease. The

In the News continued on page 44

In the News continued from page 43

Exelon® patch showed similar efficacy to the highest doses of Exelon® capsules, and the recommended dose (9.5 mg/24 hr) was generally well tolerated by patients.

The U.S. Food and Drug Administration also approved the use of the Exelon® patch in treating patients with mild to moderate Parkinson's disease dementia. Parkinson's disease is a chronic and progressive neurological condition that affects approximately 1.5 million people in the United States. Parkinson's disease dementia is a distinct and common disorder, one characterized by impairments in executive function, memory retrieval, and attention, in patients with an established diagnosis of Parkinson's disease for at least two years. Two of five people with Parkinson's disease are estimated to have Parkinson's disease dementia. For more information, visit www.ExelonPatch.com.

Magnetic Nanoparticles Show Promise in Targeted Drug Delivery

June 27, 2006 – Researchers have developed a new nanocarrier system for the delivery of drugs that contain iron and so can be directed by a magnetic field to specific areas of the body, a technology that could prove invaluable in the treatment of diseases such as cancer. The new method, developed by scientists at the University of Buffalo (UB) and recently published in *Molecular Pharmaceutics*, may lead to treatments that exploit the advantages of photodynamic therapy (PDT) and have the potential to reduce drug accumulation in normal tissues. Not only does the new system allow the guided and precise delivery of drugs to chosen areas of the body (e.g., a tumor), avoiding serious side effects, it also enhances the cellular uptake of the PDT drugs it transfers.

For their drug delivery vehicle, researchers used polymer micelles, which are nanosized, water-dispersible clusters of polymeric molecules and so are excellent nanocarriers for PDT drugs, which are mostly water insoluble. Along with the photodynamic drug, they encapsulated inside the nanocarriers iron oxide nanoparticles, which allowed them to respond to externally applied magnetic fields. "This is a novel way to enhance drug delivery to cells," said Paras Prasad, executive director of the UB Institute for Lasers, Photonics and Biophotonics. "The externally applied magnetic field acted as a kind of remote control, directing the nanocarriers to the targeted area in the cell culture."

In the experiments, nanocarriers were efficiently taken up *in vitro* by cultured tumor cells in the area exposed to the magnetic field, as demonstrated by confocal microscopy. Once the magnetic field was applied, the concentration of drug inside the tumor cells in the target area increased. "The magnetically guided drug delivery would allow for the use of lower concentrations of the drug to deliver a therapeutic dose, thus significantly reducing the amount of PDT drug that accumulates in normal tissue," said Prasad. "Because the nanocarriers proved to be significantly stable and because they retained the PDT drugs, we are optimistic that they will be able to deliver a wide range of therapies to tumors or other disease sites in the body without any significant loss in the circulatory system or in normal tissues."

While the team demonstrated their method with PDT drugs, Prasad said the technique would be useful in delivering gene therapy, chemotherapy, or practically any kind of pharmaceutical treatment into cells. Preliminary studies in live animals have indicated that an applied magnetic field can effect a localized accumulation in the tumor site, and the team is beginning *in vivo* studies on the new drug delivery method.

Respirics to Sell off MD Turbo Technology

June 14, 2007 – U.S. pulmonary drug delivery specialist Respirics has decided to sell its assets relating to its MD Turbo product to focus on its Acu-Breathe powder inhaler platform. MD Turbo is the company's first commercial product and is a companion device to assist patients who use pressurized metered dose inhalers (pMDI) for asthma and chronic obstructive pulmonary disease (COPD). According to the company, up to 70% of patients are unable to coordinate their inhalation with the firing of their pMDI canister, which leads to them receiving inappropriate dosages from their inhaler. The MD Turbo relieves this problem by coordinating MDI actuation with the patient's breath using the company's i-Point technology (predetermined inspiratory pressure activation). "MD Turbo is a helpful product and we've received a lot of very positive feedback about the value it can bring to patients who use inhalers," said Gilbert Mott, CEO of Respirics. "The product has been on the market for a year, and we believe it deserves to be in the hands of a company with resources to vigorously promote it. Consequently, we've decided to sell MD Turbo so the product can receive the attention it merits." The MD Turbo, which was cleared by the U.S. Food and Drug Administration (FDA) in 2005, also keeps tabs on the number of doses remaining in a wide range of inhalers.

In March 2003, the FDA made it mandatory for new pMDIs to incorporate dose counters or indicator mechanisms, making this second feature invaluable for those companies who do not want to redesign their pMDIs. After the company has found a new home for its MD Turbo product, it will focus on solely its latest product, the Acu-Breathe dry powder inhaler.

Dry powder inhalers have become the fastest growing segment of the dynamic respiratory pharmaceutical industry, accounting for nearly 50% of the U.S. market. These inhalers traditionally have a major drawback in that the dose received varies with the intensity of the patient's breath. According to Respirics, the Acu-Breathe products also use the i-Point technology to offer "improved delivery consistency and efficiency" by not allowing a dose to be released until the user achieves a set inhalation flow rate. The company claims that the Acu-Breathe is capable of delivering two drugs simultaneously to improve customer compliance, as well as to target drug delivery to either the upper or lower airways using an adjustable flow-rate trigger point.

Oral Sleep Spray Gets the Nod

June 6, 2007 – U.S. pharmaceutical oral spray formulation company Novadel has announced results from two studies comparing its zolpidem oral spray to Sanofi-Aventis' Ambien (zolpidem tartrate) tablets in the treatment of

insomnia. The company found that people fell asleep quicker when taking an oral spray than when taking a tablet and reached the land of nod faster with the lower dose spray than the higher dose tablet. "The oral spray enhances the performance of the product and makes it better," Novadel President and Chief Executive Jan Egberts told US-PharmaTechnologist.com.

Because it is absorbed straight into the blood stream via the oral mucosa, the spray has a much faster action than the tablet, which is more slowly absorbed after being dissolved in the stomach. Furthermore, the absorption rate means a lower drug dose is needed for a therapeutic result, Egberts said. "These positive results for zolpidem oral spray further demonstrate the potential for Novadel's technology to create meaningful improvements in the performance and ease of administration of widely used pharmaceuticals."

The two studies compared 5- and 10-mg doses of zolpidem oral spray with comparable doses of Ambien tablets in healthy volunteers and then 5-mg doses of zolpidem oral spray with 5-mg Ambien tablets in elderly, healthy volunteers.

Available in 6.25- and 12.5-mg strengths, Ambien CR consists of a coated two-layer tablet. While one layer releases the drug immediately, the other has a much slower release. Egberts believed the oral spray still outperformed Ambien CR because the spray contained a much lower drug dose.

Inhaler Device for Premature Ejaculation

May 24, 2007 – U.K. pulmonary drug development company Vectura has announced a potential breakthrough for the treatment of the strikingly common sexual dysfunction premature ejaculation, which affects 30% of men at some time in their life, after receiving successful results in its Phase IIa proof-of-concept clinical study.

By simply inhaling Vectura's product VR776, patients demonstrated a clinical effect within 15 min of dosing and an improvement in the time it took for ejaculation within the vagina, known as intravaginal ejaculatory latency time (IVELT). Not only is this exciting news for the some 50 million men affected in Europe and the United States who have no approved product to turn to, but the novel system by which the drug is delivered means the drug does not have to be taken 6 hr before intimacy, which would be the case if the treatment was in pill form.

Using Vectura's Aspirair dry powder inhaler (DPI), a patent-protected single-unit dose DPI, VR776 can be delivered with high lung penetration and rapid delivery to the bloodstream. Vectura believes the device to be conveniently sized and simple to use compared with other inhalers.

The inhaler works by generating an aerosol plume, triggered by a patient's inhalation, which is slower than most spray-type active inhalers currently available. This means that the amount of powder that is unintentionally deposited in the mouth and throat is reduced. VR776, a proprietary formulation of a centrally acting undisclosed drug that works in the brain to delay ejaculation, is formulated using PowderHale, a patented technology optimizing the delivery of dry powders. Typically, dry powder inhaled formulations have limited penetration to the lungs, but PowderHale delivers a consistent fine particle dose of the drug to the lung with high penetration by modifying the interactive forces holding together the active drug particle and carrier particles.

Vectura is also developing VR004, an inhaled systemic product for treating erectile dysfunction. Successful Phase IIb clinical trials have been completed, and Vectura is now seeking licensing partners for the product.

New Insulin Product Takes the Nasal Route

May 23, 2007 – NanoDerma, a young Israeli company specializing in advanced transdermal and intradermal formulations, has recently been directing its expertise toward an intranasal insulin product amid growing interest in alternative insulin delivery techniques that avoid the traditional needle-based approach. Although nasal drug delivery systems have been around for a while, there have been limitations in the technique due to low delivery payload, poor reproducibility, and mucosal irritation. NanoDerma has developed a drug delivery platform based on microemulsion technology that appears to combat these issues and make it a viable option for insulin delivery for treatment of diabetes.

The system is made up of water, oil, surfactant(s), and co-surfactant and is based on nano-droplets of 10–50 nm that form a viscous, semi-solid or homogenous liquid gel in the nostril. The system can incorporate "almost any lipophilic and hydrophilic compound as well as large molecules," says the company, and also offers other advantages, with no chemical penetration/absorption enhancers, alcohol, or other irritating constituents. "The NanoEmulsion technology has been shown to successfully deliver various drugs through the skin at higher rates and extents relative to the existing corresponding products in the market," says Amnon Sintov, NanoDermo vice president of R&D. "It offers complete incorporation and solubility of large amounts of almost any drug and biopharmaceutical."

With non-injected delivery of large molecules such as insulin having been NanoDerma's main objective over the last year, the company has high hopes for its intranasal insulin formulation. Already having completed pharmacokinetic and pharmacodynamic studies in rabbits, results for the new formulation are looking very promising. Due to the high payload possible with the company's drug delivery technology, there is no need to apply more than 100 µL to achieve the required hypoglycemic effect, a volume unlikely to cause any irritation in users and, therefore, aid in compliance. The NanoEmulsion formulation also resulted in plasma glucose levels similar to injectable administrations, and although insulin was quickly eliminated from the plasma after 1 hr, the hypoglycemic effect lasted "much longer" after the nasal administration, said Levy.

NanoDerma isn't the only company taking the nasal route to break into the insulin-delivery market. Bentley Pharmaceuticals, for example, currently has a recombinant intranasal insulin spray for postprandial hyperglycemia in Phase II trials in the United States, although unlike the NanoDerma product it contains a physiological absorption enhancer. The

In the News continued on page 46

In the News continued from page 45

U.S. firm Nastech is also in the process of developing a nasal insulin product for type I diabetes, and in December reported positive results from a Phase I trial compared with Exubera inhalable powder and injectable insulin.

Australian Spin-offs Pursuing Nanotechnology Innovations

May 15, 2007 – A transdermal patch for needle-free delivery of insulin and a diagnostic test for rapid detection of meningococcal disease are among the products under development by two new Australian companies set up to commercialize the research outcomes of Nanotechnology Victoria (NanoVic). The spin-offs, Interstitial NanoSystems (Interstitial NS) and Quintain NanoSystems (Quintain NS), were announced by Victorian Premier Steve Bracks and Minister for Innovation John Brumby at the BIO2007 Conference in Boston, Massachusetts, in May. Each has a portfolio of four complementary projects to which NanoVic owns the commercial rights. Each is seeking between A$20 and A$25 million (€12.3 and €15.4 million) to take these products to market.

The portfolios, which include transdermal and pulmonary nanoparticle delivery for large-molecule drugs (Interstitial NS), as well as nanoparticle-based diagnostic imaging and NanoArray diagnostic biochips for high-sensitivity laboratory-based diagnosis (Quintain NS), have been built around strategic investment of nearly A$14 million by NanoVic and more than a dozen partners since 2004. The aim is to market the resulting products in Australia, the United States, and Europe once they have been through the necessary clinical trials and regulatory approvals.

Three leading Victorian institutions, Monash University, RMIT University, and Swinburne University of Technology, are shareholders in, and research and technology providers to, NanoVic. Described as "the key organization for delivering nanotechnology research outcomes" to industry in the South East Australian state, NanoVic also has financial backing from the state government of Victoria.

Australia Scientists Announce Cancer Drug Breakthrough

AFP: May 11, 2007 – Australian scientists announced they have developed a cancer treatment that could deliver lethal doses of drugs to tumors without the usual harmful side effects, such as nausea and hair loss. Research scientist Jennifer MacDiarmid said the cutting-edge technique uses nanotechnology to create particles that directly attack cancer cells with a "lethal payload" of drugs, without flooding the body with toxic chemicals.

Treatments such as chemotherapy typically involve subjecting the patient's entire body to the powerful drugs to kill the cancer, causing debilitating side effects that the new, targeted technique would eliminate. "Your hair wouldn't fall out, you wouldn't throw up…some chemotherapy is life-threatening in itself," MacDiarmid told AFP. MacDiarmid said scientists at Sydney-based biotechnology company EnGeneIC, where she is a managing director, used a bacteria cell stripped of its reproductive powers to develop a particle capable of carrying any chemotherapy drug. The nano-cell, which is about one-fifth the size of a normal cell, is then tagged with antibodies that are attracted to cancerous tumors. Once the cell hits the cancer, the drug is released directly into the malignant growth. "There is no other system where you can get so much drug concentrated into a little parcel," MacDiarmid stated.

The results of animal trials published in the U.S.-based journal *Cancer Cell* show that the technique has reduced tumors in animals without toxic side effects while using only a very small amount of drugs. MacDiarmid said the treatment could potentially be used on any solid tumors, including those in the breasts, ovaries, colon, and lungs. In the future, the treatment could allow for the creation of customized drug "cocktails" to be used on patients to counter drug resistance and could lower costs as smaller amounts of drugs would be needed, she said. The team hopes to start human trials by the end of this year.

Schwarz Parkinson's Patch

May 10, 2007 – Schwarz Pharma's foray into the central nervous system disorder market is beginning to pay serious dividends as the firm's groundbreaking transdermal patch for Parkinson's continues to prove a success story, now gaining approval in the U.S. market. The company's Neupro transdermal patch, which delivers a continuous flow of the anti-Parkinson's drug rotigotine over a 24-hr period, has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of signs and symptoms of early-stage Parkinson's, with a supplemental new drug application for the advanced stage of the disease due to be filed later this year.

Rotigotine belongs to a class of drugs known as non-ergolinic dopamine agonists, the latest generation of dopamine agents. Dopamine acts as a messenger substance between the brain and nerve cells, but Parkinson's patients do not produce enough of the chemical, resulting in transmission problems between the brain and the body and leading to muscular tremors, weakness, and impaired mobility. Rotigotine and other non-ergolinic agents mimic the action of dopamine, and as such reduce the symptoms of Parkinson's. Where Schwarz's product, unlike the only other two non-ergolinic products currently available, is delivered transdermally, offering a wealth of advantages over rival products.

Mirapex (pramipexole) by Boehringer Ingelheim and Requip (ropinerole) from GlaxoSmithKline are the only other non-ergolinic products currently available to Parkinson's patients, and both are delivered orally at least three times a day. Neupro, in contrast, is the first once-daily, continuous delivery transdermal product, and upon its launch in the European Union last year seriously outstripped its two competitors and outperformed even Schwarz's estimates.

The transdermal product solves a number of problems associated with current Parkinson's treatments. The other products currently available in the class require several doses a day, whereas Neupro can simply be stuck on the skin and left to release a continuous flow of the drug. A common problem with the multiple-dose regime used with orally delivered products is what is known as the "roller coaster" effect—patients experience fluctuations in the levels of treatment as earlier doses

begin to wear off or as the most recent dose kicks in. To try and combat this unpleasant experience, many patients cut their pills in half and take them even more frequently to try and iron out variations throughout the day. Compounding this problem, patients are rarely able to take their treatment overnight without interrupting sleeping patterns, so they often wake up stiff and suffering the full onslaught of Parkinson's symptoms.

The transdermal patch appears to solve almost all of these common issues and has proved popular with patients. "The continuous release patch is the only transdermal product available in this class of drugs," Antje Witte of Schwarz Pharma told in-PharmaTechnologist.com. "It's a once daily product that can work both day and night – it's almost as good as our healthy brains."

Although the patch has been available in Europe for both early-stage Parkinson's and in combination with levodopa for advanced Parkinson's, the U.S. approval is currently for early stage only. Schwarz decided to push ahead with the early-stage product rather than waiting for approval for advanced Parkinson's to get the product onto the U.S. market as soon as possible, according to Witte. Once approval has been granted in the United States for use of the patch for treatment of late-stage Parkinson's, Schwarz Pharma has estimated EU and U.S. sales of the product for both indications to hit around $350 million.

"Parkinson's is a very difficult disease," said Witte, "and it can be a very conservative and hesitant market." Despite this, with professional opinion leaning toward recommending non-ergolinic agents for newly diagnosed patients and the growing market share reflecting this opinion, Schwarz would seem to be in a prime position to reap the rewards of a product that offers such distinct administration advantages over its current competitors.

Successful Clinical Trial of Chrono Therapeutic's Pulsatile Transdermal Drug/Device Combination Product ChronoDose™

PR Newswire: May 3, 2007, BASEL, Switzerland, and TRENTON, N.J. – Chrono Therapeutics Inc. (CTI) has announced the successful completion of its Phase I human clinical trial of its ChronoDose™ system. The trial proved the functionality of CTI's programmable, pulsatile, and passive transdermal drug delivery device in humans. The trial was conducted between February and April 2007 at the University Hospital Basel, Switzerland, Division of Clinical Pharmacology and Toxicology. Dr. Georgios Imanidis, Ph.D., of the University of Basel was the principal investigator on behalf of CTI. This study was an open, randomized, three-period, single-center, dose-escalation study. Thirty-six independent human transdermal tests were conducted on male volunteers using wristwatch-like ChronoDose™ devices.

The trial successfully proved the efficacy of the device on human subjects using its model drug compound. The dose-escalation trial showed statistically significant modulation and control of the dosing profiles. Using low, medium, and high concentrations, for 16 hr, the model drug permeated each subject's skin on multiple occasions, resulting in clear and distinct peaks and troughs of therapeutically effective and well-targeted blood plasma concentration levels. Local and systemic tolerability of the model drug after its transdermal administration was better than planned.

Dr. Imanidis commented, "CTI has for the first time in transdermal drug delivery history successfully completed a significant human trial with a passive, automated and programmable multiple dosing transdermal device system. We are extremely pleased with the excellent results." Guy DiPierro, CEO and president of CTI noted, "This solid and convincing clinical data along with initial human data generated last summer will help us to rapidly commercialize our initial drug product. We are particularly pleased that ChronoDose™ produced targeted blood plasma concentrations as accurately as it did and at the intended time periods."

Molecular Syringe Delivers Drug into Cells

May 2, 2007 – A "homing" protein fragment that can track down tumors in the body has been developed to deliver imaging agents or anti-cancer therapies to cells. Researchers from Yale University and the University of Rhode Island in the United States have used the pHLIP (pH low insertion peptide) protein fragment to target the acidic tissue that builds up in tumors and inflammation sites observed in arthritis patients.

After attaching itself to a cell membrane, the acidic conditions surrounding tumor cells cause the protein to change conformation and insert itself across the cell membrane and inject its payload. The use of the pHLIP protein fragment in delivering drugs or imaging agents to tumors will be published in an upcoming issue of the *Proceedings of National Academy of Sciences*. "Since the mechanism is general, and since even very small tumors can be targeted, there is an exciting array of possible applications for pHLIP," said Prof. Donald Engelman, of Yale University and a co-author of the paper. "We are very excited by the possibilities for both imaging and treating tumors."

This research used near-infrared (NIR) fluorescence to follow the accumulation of fluorescently labeled pHLIP at the site of acidic tissues in mouse cancer and inflammatory arthritis models. Light in the NIR region can travel through tissue for several centimeters and allows the imaging of tumors or plaques in living models to allow disease progression to be monitored. The technique was so effective that it enabled imaging of tumor spots of various sizes—even those that were too small to detect visually. An earlier paper published by the groups in *Biochemistry* showed that at low pH, pHLIP can release cell-impermeable molecules into the cytoplasm inside acidic cells.

"pHLIP acts as a molecular nanosyringe, inserting itself into the cell membrane and injecting compounds into [the] cell," said co-author Yana Reshetnyak (University of Rhode Island). "The transported molecules can be therapeutic or toxic to the cell, depending on the intended outcome – for treating cancer; the idea is to cause cell death."

Approval Triggers $19 Million Milestone Payment

Business Wire: April 30, 2007, ALAMEDA, Calif. – InSite Vision

In the News continued on page 48

In the News continued from page 47

Incorporated (AMEX: ISV), an ophthalmic therapeutics, diagnostics, and drug delivery company, has announced that the U.S. Food & Drug Administration (FDA) has approved InSite's New Drug Application (NDA) for AzaSite (azithromycin 1% ophthalmic solution) for the treatment of bacterial conjunctivitis. AzaSite is formulated with DuraSite, InSite Vision's patented drug delivery vehicle that enhances the retention time of the antibiotic on the surface of the eye.

AzaSite was shown to be safe and effective in two Phase 3 clinical trials conducted with more than 1,400 patients in the United States and Latin America. In these clinical studies, which were designed and conducted in concert with Mark Abelson, M.D. and Ophthalmic Research Associates, AzaSite was administered twice daily on the first two days, then once daily on days 3–5. The results demonstrated that AzaSite provided clinically and statistically significant improvements in clinical resolution of symptoms and bacterial eradication compared with a placebo and was equivalent in clinical resolution and bacterial eradication compared with tobramycin administered four times per day for 5 days. The principal investigators, Drs. Warren Heller and Eugene Protzko, respectively, formally presented these study results at the 2006 American Academy of Ophthalmology Annual Meeting and the Association for Research in Vision and Ophthalmology Annual Meeting.

"We are truly delighted with the AzaSite product approval," said S. Kumar Chandrasekaran, Ph.D., InSite Vision's chief executive officer. "This approval and our related commercialization agreement with Inspire Pharmaceuticals for the U.S. and Canada represent major accomplishments for our company and will now automatically trigger the milestone payment of $19 million. Our objective is to provide both the patient and the physician with a convenient and highly effective alternative for the treatment of bacterial conjunctivitis. We expect Inspire Pharmaceuticals to utilize an expanded sales force to launch AzaSite later this year."

DelSite Smells Success for Novel Flu Vaccine

April 23, 2007 – A nasal powder flu vaccine is one step closer, as DelSite Biotechnologies has announced that it has found an antigen to use with its novel drug delivery system. The company has secured a source of influenza antigen, allowing it to push forward with plans for Phase I clinical trials of the flu vaccine based on the firm's innovative GelVac dry powder technology. This will be the first powder-based nasal flu vaccine to be used in a human trial, the company claims, although a liquid flu vaccine formulation, MedImmune's Flumist, has been on the market since 2003 and was the first needle-free flu vaccine to be launched.

Despite the availability if Flumist, there seems to be room in the market for another non-injectable candidate. MedImmune's product has failed to make significant inroads into the injectable seasonal flu vaccine market and remains unprofitable, according to analyst comments regarding a proposed $15 billion acquisition of the firm by AstraZeneca.

The GelVac powder is based on DelSite's GelSite natural carbohydrate polymer product. When the powder comes into contact with nasal fluids it forms a wet, mucoadhesive gel that entraps the vaccine antigen. According to the company, this provides a mechanism for prolonged exposure of the antigen to the nasal lymphoid tissue, potentially enhancing the protective immune response.

The vaccine itself boasts several attractive features that could make it particularly appealing as an option to meets the needs for pandemic preparedness and epidemic control, according to DelSite. For example, the vaccine is stable at room temperature and, therefore, does not require freezing or cold chain distribution systems, making it a viable option in developing, as well as developed, countries. The vaccine also has a prolonged shelf life, having successfully been stored at room temperature for over two years, which is another point in its favor as a candidate for pandemic stockpiling. The vaccine itself is also manufactured without the need for organic solvents and uses no preservatives. In addition, the powder vaccine can be administered intranasally without the need for needles, making it perhaps more consumer friendly, but the product can also be reconstituted with sterile water and delivered via a standard injection, thus offering a choice of delivery method.

According to DelSite, the vaccine also boasts therapeutic advantages that make it a superior choice compared with standard vaccines. As a nasal vaccine, the GelVac system provides both local mucosal immunity in the nasal passage, as well as systemic protection throughout the body. Injectable vaccines, on the other hand, tend to only induce a systemic immune response. This double-immunity feature and the speed with which the nasal passage becomes protected could prove particularly useful when immunizing children and the elderly, who may have immature or weakened immune systems. The company also asserts that its intranasal vaccination could confer protection at other mucosal sites, such as the lungs or intestines, and provide cross-protection against variant strains through lymphocyte trafficking within the body.

DelSite completed pre-investigational new drug (IND) talks with the U.S. Food and Drug Administration (FDA) covering its nasal powder vaccine during November of last year and anticipates the IND application to be filed in late 2007 for clinical trials in the United States.

Endo Notified Zingo Not Generic

AP: April 10, 2007, CHADDS FORD, Pa. – Drug maker Endo Pharmaceuticals Holdings Inc. has announce that biotech drug maker Anesiva Inc. notified the company its needle puncture anesthetic is not a generic substitute for Endo's pain products. Endo makes the pain patches Lidoderm and Synera. South San Francisco, California-based Anesiva notified Endo of its Food and Drug Administration application referring to patents covering Lidoderm and Synera. Unlike these lidocaine patches, Anesiva's proposed product, Zingo, shoots lidocaine into the skin using accelerated gas particles. However, while Zingo uses a different delivery system, Endo believes that Zingo may compete with Synera because of the similar indication, to numb the skin before a needle stick. The FDA began reviewing an application for Zingo in late January. Endo said it will continue monitoring notices from Anesiva. ■

Developing Education to Fit Your Needs

Workshops and Symposia

November 2–3, 2007
NanoDDS'07 – Nanomedicine and Drug Delivery Symposium
Northeastern University
Boston, Massachusetts, U.S.A.

November 9–10, 2007
Development and Regulatory Challenges for
Controlled Release Formulations Workshop
CRS Workshop co-sponsored by AAPS
San Diego Convention Center
San Diego, California, U.S.A.

December 9, 2007
CRS Australian Chapter 1st AUS-CRS Symposium
Held in conjunction with the
Australasian Pharmaceutical Science Association Annual Meeting
Manly Pacific Hotel
Sydney, Australia

Educational Workshops

These workshops will precede the 35th Annual Meeting & Exposition
of the Controlled Release Society at the Hilton New York.

July 12, 2008
Delivery of Biologics with Novel Polymeric Constructs
Chair: David Brayden, University College Dublin, Ireland

July 12–13, 2008
Oral Drug Delivery: Challenging Patient Groups
Chairs: Daniel Bar-Shalom of Eaglet A/S, Denmark
Brigitte Skalsky, Degussa, Germany

July 12–13, 2008
Strategies to Advance the Bioavailability of Low Solubility Drugs
Chairs: Yvonne Perrie, Aston University, U.K.
Thomas Rades, University of Otago, New Zealand

Controlled Release Society
www.controlledreleasesociety.org

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

calendar of events

who…what…where…when

NanoDDS '07 – Nanomedicine and Drug Delivery Symposium

November 2-3, 2007
Northeastern University
Boston, Massachusetts, USA
www.nanodds.org

CRS Education Committee Satellite Workshop

November 9-10, 2007
San Diego Convention Center
San Diego, California, USA
www.aapspharmaceutica.com/meetings/annualmeet/am07/

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

CRS Australian Chapter 1st AUS-CRS Symposium

December 9, 2007
Manly Pacific Hotel
Sydney, Australia
www.apsaconference.info

9th US-Japan Symposium on Drug Delivery

December 16-20, 2007
Westin Maui
Lahaina, Hawaii, USA
http://web.mit.edu/langerlab/9thsymposium/

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

36th Annual Meeting of the Controlled Release Society

July 18-22, 2009
MIC Milano Convention Centre
Milan, Italy
www.controlledreleasesociety.org
Tel: 651-454-7250