

Volume 26 • Number 1 • 2009

What's Inside

What Is a Bioactive?

Interview with Nicholas Peppas

Stratum Corneum Hydration and Transcutaneous Vaccine Antigen Penetration

Raman Microscopy Imaging of Nanocarrier Systems

'Microbes in a Mug' Competition

Quality by Design

Calling All Protégés!

Pharmaceutical Sciences and Biotechnology Patents



The industry's only publication entirely devoted to drug delivery and development now has a new website and eNewsletter!

www.DrugDeliveryTech.com

Drug Delivery[®] Technology

including
SPECIALTY PHARMA
Specialty Pharmaceuticals

HOME | SUBSCRIPTION SERVICES | ADVERTISING OPPORTUNITIES | ABOUT US | CONTACT US

MAGAZINE



CURRENT ISSUE

BACK ISSUES

EDITORIAL CALENDAR

SUBMISSION GUIDELINES

MEDIA PLANNER

View our current issue or the back issue library

YOUR AD HERE

2009 Media Planner for Advertisers

ONLINE NEWSLETTER

Drug Delivery **WEEKLY**
Technology
including
SPECIALTY PHARMA
Specialty Pharmaceuticals

BREAKING NEWS

SPONSORED BY CATALENT

Acusphere Licenses Hydrophobic...

Avant Therapeutics Launches...

Drug Delivery Science Receives...

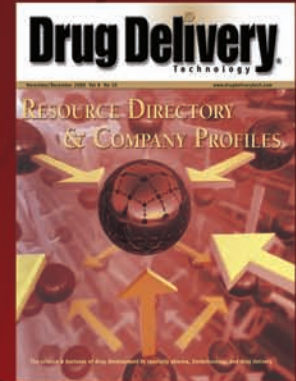
Euroand Announces Positive...

Tekmira Pharmaceuticals & Protiva...

The latest news about alliances, milestones & technology breakthroughs

YOUR AD HERE

RESOURCE DIRECTORY



COMPANY PROFILES

DRUG DELIVERY TECHNOLOGIES

EXCIPIENT, POLYMERS, LIPOSOMES & LIPIDS

CONTRACT PHARMACEUTICAL & BIOLOGICAL DEVELOPMENT SERVICES

MACHINERY & LABORATORY EQUIPMENT AND SOFTWARE

Company profiles of the industries leading innovators

YOUR AD HERE

Visit our Global Resource Directory

For more information on print and online advertising opportunities call

East & Midwest - Victoria Geis
703-212-7735 - vgeis@drugdeliverytech.com

West - Warren DeGraff
415-721-0664 - wjdegtraff@drugdeliverytech.com

International - Ralph Vitaro
973-299-1200 - rvitaro@drugdeliverytech.com



Steven Giannos
Editor



Bozena Michniak-Kohn
Editor



Yvonne Perrie
Editor



Rod Walker
Editor



Jamileh Lakkis
Editorial Board



Arlene McDowell
Editorial Board



Rajarajeswari Sivalenka
Editorial Board

Table of Contents

From the Editor	2
From the President	3
Forum	
Anyway, What Is a Bioactive?	4
Interview	
Nicholas A. Peppas Elected to the Institute of Medicine	6
Welcome New Members	9
Scientifically Speaking	
Mechanistic Insights into Stratum Corneum Hydration and Implications for Transcutaneous Vaccine Antigen Penetration	10
Raman Microscopy Imaging of Nanocarrier Systems for Cellular Uptake and Trafficking	13
Microbes in a Mug Research Competition	15
36th CRS Annual Meeting & Exposition	
Back in Europe	16
From the Vet Group	
Quality by Design	22
Young Scientist Committee	
Young Scientists Mentorship Program—Calling All Protégés	24
Chapter News	
Report on the 2nd AUS-CRS Annual Meeting	26
CRS-Illinois Student Chapter Holds Social Event	27
CRS New Zealand and Australian Chapters Hold Joint Workshop on Peptide and Protein Bioactives—Stability and Delivery	27
CRS Committee Corner	
C&DP Committee	29
JCR Highlights	
Top Five Downloaded Research and Review Articles in the <i>Journal of Controlled Release</i>	30
Patent Watch	
Pharmaceutical Sciences and Biotechnology	32
In the News	42
Event Calendar	Cover 4

Advertisers' Index

Drug Delivery Technology	Cover 2
Scopus	5
Texas A&M Health Science Center College of Medicine	29



Arlene McDowell
University of Otago, School of Pharmacy
Dunedin, New Zealand

Editors

Steven Giannos
Bozena Michniak-Kohn
Yvonne Perrie
Rod Walker

Editorial Board

Jamileh Lakkis (C&DP)
Arlene McDowell (Vet Group)
Rajarajeswari Sivalenka (C&DP)

Publications Committee Chair

Ijeoma Uchegbu

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

Newsletter articles reflect only the views of the authors. Publication of articles or advertisements within the CRS Newsletter does not constitute endorsement by the Controlled Release Society or its agents of products, services, or views expressed herein. No representation is made as to the accuracy hereof and the publication is printed subject to errors and omissions.

Editorial contributions should be directed to the CRS Newsletter Editors, (CRSNewsletter@scisoc.org) and are subject to the terms and conditions of the Editorial and Publication Release. Publisher assumes no responsibility for the safety or return of artwork, photographs, or manuscripts.

Requests for advertisement placement may be directed to Debby Woodard, Business Development Department; telephone +1.651.994.3817, or e-mail at dwoodard@scisoc.org. All advertisements are subject to "General Conditions of Sale."

Unauthorized reproduction in whole or in part is prohibited. Requests for permission should be directed to the Editors at newsletter@scisoc.org.

©Copyright 2009 Controlled Release Society. All rights reserved.

Controlled Release Society
3340 Pilot Knob Road
St. Paul, MN 55121 U.S.A.

Telephone: +1.651.454.7250
Facsimile: +1.651.454.0766

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

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

Happy New Year!

Welcome to the first *CRS Newsletter* for 2009—the year of the ox I am told. You will see more of us this year, as in 2009 we have moved to producing five issues of the *CRS Newsletter*. This means we will be looking for more material to present, so we would love to hear from you if you would like to make a contribution to your newsletter. And, to our new members who have recently joined the Society, we hope you enjoy reading your first issue.

I have just been asked to come up with a name for our new research laboratory that captures the essence of what we do and what that lab is about. Not an easy thing to do when there are existing labs that have taken all the useful names, such as "Pharmaceutical Science Research Lab." The CRS Board faced the same dilemma, albeit on a larger scale, with the development of a new logo tagline that was discussed in the last issue of the newsletter by Ian Tucker and Charles Frey with their piece exploring "Does What We Release Define Us?" In this issue, a letter by Ian Tucker titled "Anyway, What Is a Bioactive?" continues the discussion of the suitability of the term bioactive in the tagline. I encourage you to share your ideas on the topic with us.

Local Chapters continue to be a very active and important part of our Society. This is evidenced in this issue of the *CRS Newsletter* in "Chapter News," with another three reports from different activities organised by the CRS Chapters in Australia, Illinois, and New Zealand during the latter part of 2008. These activities include a very successful joint meeting of the Australian and New Zealand Chapters on the stability and delivery of peptide and protein bioactives. As this issue goes to print, the New Zealand Chapter is preparing to co-host a Formulation and Delivery of Bioactives conference at the University of Otago in Dunedin.

In this issue you can also see what's hot in controlled release by reviewing the list provided in the "JCR Highlights" of the five most downloaded research and review articles published in the *Journal of Controlled Release*. We also have all our regular forums, including "Scientifically Speaking," "Patent Watch," and an interesting interview with Prof. Nicholas Peppas.

All that science should really whet your appetite for what is to come in Copenhagen at the CRS Annual Meeting & Exposition. While many of us converse throughout the year by e-mail, Skype, or phone, nothing beats talking face-to-face, and Denmark will provide a fantastic venue to catch up with colleagues and meet new ones. We hope to see you there!

On behalf of the editorial team of the *CRS Newsletter*, I wish you a happy, healthy, and successful 2009.

Best wishes,

Arlene McDowell ■



Lisbeth Illum
IDentity, Nottingham, U.K.

On behalf of the Board of Directors (BOD) of CRS, I should like to wish you all a belated very happy New Year, both in your personal lives and most certainly in your professional lives. Let us hope for a new year where the world will see peace and improved prosperity.

As mentioned in my column in the last issue of the *CRS Newsletter*, the CRS is a non-profit organization dedicated to promoting the science, technology, and innovation of delivery of bioactives for the benefit of the world population. However, the Society needs to be run on a strong business footing to provide increased value, maintain and improve the quality of the science, and increase access to scientific meetings and workshops worldwide for all members.

For this purpose, we have recently finalized a five-year strategic plan that should help us develop the Society, along the lines presented to you and discussed with you at the annual members' meeting in New York in 2008. Furthermore, we are preparing the first CRS business plan to support the strategic plan, with descriptions of a variety of initiatives and the budgets to go with them.

The strategic plan contains goals and metrics for the diversification and globalization of the Society in order for the Society to become sufficiently financially strong to support a large range of new or enlarged activities for the benefit of all members of CRS. This also means that the CRS will become less financially dependent on the annual meeting.

The executive and strategic direction of CRS is decided by the elected BOD, which carries out the vision of CRS and has the responsibility of considering the overall portfolio of products and services offered by our organization. The BOD also looks for ideas for membership products and services outside of current programs on a strategic level. The BOD is assisted in this activity by numerous committees staffed by member volunteers. The BOD depends heavily on these committees to provide input on potential strategies and background reports. The committees normally work within their individual areas of responsibility and continually make incremental changes to their ongoing programs.

The CRS Annual Meeting & Exposition is, and will remain, the flagship event and product of CRS. It is envisaged that in the next few years CRS will initiate a smaller, one to two topic-driven, second annual meeting to be held in the winter season in different parts of the world than the venue of the CRS Annual Meeting & Exposition. Other activities, such as educational workshops and satellite meetings, will be held throughout the year in concert with the CRS Annual Meeting & Exposition. CRS realizes that education is a year-round process and that not all CRS members (or those interested in delivery science) can attend the CRS Annual Meeting & Exposition. Hence, a year-

round goal of CRS will be to imbue all activities with the education, business, and spirit of the CRS Annual Meeting & Exposition, with the hope that these other strategic initiatives will encourage more involvement and participation at the CRS Annual Meeting & Exposition. The CRS will continue to hold meetings at international sites on a regular basis. While historically there is a financial disadvantage in holding annual meetings outside the United States, the CRS must maintain a regular schedule of such meetings to retain its international focus. The new envisaged activities cover an increased number of educational workshops and satellite meetings being offered around the world, CRS book publishing, new CRS journals, webcasts, a more interactive website, and increased presence in developing countries such as China and India through involvement in and support of workshops.

As I did in my last column, I again urge you to sign up to participate in the CRS Annual Meeting & Exposition in Copenhagen in July 2009. The meeting will present the newest and most exciting science in the delivery of bioactives and other functional materials, with the involvement of pharmaceutical and other companies and universities from around the world. The program of the meeting is absolutely bursting with exciting and novel topics and world-renowned speakers. A large number of abstracts have already been received.

The CRS Educational Workshop Review Committee and BOD have selected and are also offering four very exciting educational workshops in Copenhagen:

- **RNA Interference Biology and Therapeutics**, chaired by Ken Howard and Jørgen Kjems (Interdisciplinary Nanoscience Center (iNANO) at the University of Aarhus, Denmark)
- **Imaging in Drug Development**, chaired by Ole Hjelstuen (University of Tromsø/GE Healthcare, Norway) and Susanna Abrahmsén Alami (AstraZeneca, Sweden)
- **In Vivo Dissolution—Is It a Reality? Can It Be Correlated to In Vitro or In Silico Dissolution?**, chaired by Daniel Bar-Shalom (IPC International Operations A/S, Denmark) and Anette Müllertz (Bioneer:FARMA, Denmark)
- **Micro and Nano Encapsulation**, chaired by Christopher Barbe (Ceramisphere Pty Ltd, Australia) and Teresa Virgallito (Microtek Laboratories, U.S.A.)

Early-bird registration is open now and will be available through May 4, 2009, at the reduced rates. Make your decision now to join the meeting and mark the dates July 18–22, 2009, in your diary. Register by May 4, 2009 to receive the best CRS member rates!

All that remains for me to say is that although the economic depression in the world is a current reality, light is ahead, and we are counting on your continued support. Have a peaceful and productive start to your New Year.

Lisbeth Illum ■

Anyway, What Is a Bioactive?

Ian Tucker
CRS Member-at-Large



Ian Tucker

In the previous issue of the *CRS Newsletter* there was a thought-provoking article on “Does What We Release Define Us?” This article was stimulated by the CRS rebranding exercise that resulted in a new logo with the tagline “Delivering Bioactives.” The article questions whether this tagline fully encapsulates all the interests of our multidisciplinary Society or whether an alternative would be better. A

strong society like the CRS encourages and expects robust, constructive, and respectful debate on relevant issues, and so I present an additional view that I hope will further the discussion.

A major issue may be that we do not have a shared understanding of what constitutes a bioactive. When choosing the tagline, the CRS Board of Directors thought a bioactive to be any compound or active that has an effect on life, that is on the “bios.” Examples ranging from the obvious to the more abstruse include

- Antigens stimulating the immune system
- Drugs with positive pharmacological effects
- Genetic materials of various types
- Antibiotics/antivirals acting against micro-organisms
- Biocides for pests of all types
- Fertilizers acting on plant life
- Perfumes/flavours stimulating smell and taste receptors
- Enzymes for both biological effects (e.g., enzyme replacement therapy) and for washing products
- Stem cells and other cells such as islet cells for insulin delivery

A glance through the program of the 2008 CRS Annual Meeting & Exposition in New York reveals examples of many of these bioactives, although not all. In the early years of the Society, there were presentations on topics such as controlled release of fertilizers, inks, and dyes. Controlled release of biocides for purposes such as antifouling paints for boats or to kill lamprey in the Great Lakes waterways was also discussed, but such topics seem to have fallen away as the Society has evolved over 35 years. Emphasis has shifted from controlled release to temporal and spatial control of delivery.

There were a few papers at the 2008 annual meeting that did not relate to delivery of bioactives. Gas-filled liposomes for oil recovery were described, although these could have biological applications given that another paper dealt with chitosan nanobubbles containing oxygen for hypoxic tissue. Another dealt with durable microcapsules for non-release applications, and although I wonder whether the founders of the CRS envisioned non-release to fall within controlled release technologies, permanent encapsulation of contrast agents to target specific tissues for imaging purposes seems a natural fit with the CRS.

Although it is accepted that papers dealing with novel biomaterials and nanotechnologies are relevant given their future applications to delivery of bioactives, papers on scaffolds for tissue engineering appear dubious at first thought. However, it can be argued, reasonably, that although a scaffold may not contain any bioactive, it does direct the spatial movement of endogenous bioactives and, therefore, in this sense, is delivering bioactives.

It would appear that the great majority of papers at CRS annual meetings fall under the tagline, “Delivering Bioactives,” including many from the Consumer and Diversified

Products section. There are some, however, for which the link is tenuous, e.g., dyes for textiles and cosmeceuticals are examples. However, even for these an indirect effect on life can be posited through the senses of sight and touch. The controlled delivery of oils to the skin, for example, can affect the psychological (and physical) behaviours of both men and women! Is this sufficient for all members to accept the tagline as all-embracing, or are there still some who would feel excluded?

What are your thoughts?
Share your opinion on this by
visiting the CRS website at
[www.controlledreleasesociety.org/
customer/source/communities/
communityHomePage.cfm?
section= Home&CmtyId=5](http://www.controlledreleasesociety.org/customer/source/communities/communityHomePage.cfm?section=Home&CmtyId=5)

It may not be possible to compose a tagline that would be accepted by all; few things in life are. I have argued, however, that “Delivering Bioactives” is a reasonable tagline that succinctly encapsulates our science and technology, which is aimed at improving the quality of life; however, I am open to being convinced otherwise, and I look forward to feedback from members on this debate. ■

-
Scopus is the largest abstract and citation
database of peer-reviewed literature and
quality web sources with smart tools to track,
analyze and visualize research.
-

-
enrich
your
experience
-

-
www.scopus.com
-

refine your research
SCOPUS™

Nicholas A. Peppas Elected to the Institute of Medicine

Brian Kilfoyle and Bozena Michniak-Kohn

Rutgers–The State University of New Jersey, Ernest Mario School of Pharmacy, U.S.A.



Nicholas A. Peppas

Nicholas A. Peppas is the Fletcher Stuckey Pratt Chair in Chemical Engineering, Biomedical Engineering, and Pharmacy at the University of Texas at Austin, U.S.A. He received a Dipl. Eng. degree from the National Technical University of Athens, Greece, in 1971 and his doctorate (Sc.D.) in chemical engineering from the Massachusetts Institute of Technology, U.S.A., in 1973. He joined the faculty at the University of Texas at Austin in 2003 and directs the

Laboratory of Biomaterials, Drug Delivery, Bionanotechnology and Molecular Recognition.

Dr. Peppas has received international recognition in numerous fields, including biomaterials, bionanotechnology, and drug delivery. He has made significant advances in the field of drug delivery systems, making it into a mature area of scholarly and applied research. He is responsible for setting theories and equations that explain diffusion in controlled release devices (Peppas equation) and transport through biomaterials (Peppas-Reinhart theory, Brannon-Peppas theory, Huang-Peppas theory, and Sahlin-Peppas equation). The impact of these theories and equations can best be demonstrated by the number of times they are cited throughout the literature, as Dr. Peppas is recognized as one of the most cited authors in the field.

Dr. Peppas and his laboratory are making key advancements in many fields. Their earliest oral delivery systems for theophylline and proxiphylline were developed in the late 1970s. Recently, they have received attention for their development of an insulin capsule to replace insulin injections for diabetics. These devices allow oral administration of insulin and protection of the protein from the harsh environments of the stomach and small intestine while exhibiting high bioavailability. This technology, one of the first to be effective for the oral delivery of proteins, is now being applied to the delivery of drugs in osteoporosis, cancer, and multiple sclerosis therapies. Other devices the Peppas group has developed include intraocular lenses; materials for cartilage replacement, artificial heart linings, and vocal cord reconstruction; and biogels for release of growth factors to improve wound healing.

In October 2008, Dr. Peppas was elected to the Institute of Medicine (IOM) of the National Academies, U.S.A. The IOM elects members based on their professional achievements and for “major contributions to the advancement of the medical sciences, health care, and public health.” Appointment to the IOM is one of the highest honors a scientist or engineer in the medical

sciences can receive. Established in 1970 by the U.S. National Academy of Sciences, the institute provides unbiased, evidence-based analysis and recommendations on issues pertaining to biomedical science, medicine, and health.

Dr. Peppas is a member of several other academies, including the National Academy of Engineering, the French Academy of Pharmacy, and the Academy of Medicine, Engineering and Science of Texas. He was the elected chair of College of Fellows, American Institute of Medical and Biological Engineering in 2006, president of CRS in 1987–1988, and President of the Society for Biomaterials in 2002–2003. He has received many awards throughout his career, including the Founders, William H. Walker, Jay Bailey, and Bioengineering and Materials Awards from the American Institute of Chemical Engineers; the Pierre Galetti Award from AIMBE; the Founders and Clemson Awards of the Society for Biomaterials; the Dale E. Wurster Award in Pharmaceutics and the Pharmaceutical Technology Award from the American Association of Pharmaceutical Scientists; and the Eurand Award for Outstanding Contributions in Oral Drug Delivery from CRS.



Ken Diller (chair of Biomedical Engineering) offers a toast during the reception held in honor of Nicholas Peppas' election to the Institute of Medicine of the National Academies of Science (November 24, 2008). (Photo by Dr. Jack Hart, BME University of Texas)

Although Dr. Peppas has authored well over 1,000 publications and is the inventor on 35 patents, he still finds time for numerous hobbies outside of his scientific and academic endeavors. He has a love of Byzantine and European history and a passion for opera. He has published critiques, essays, and articles on these subjects and has even published two books (*Vasso Argyris: The Great Greek Tenor of the Inter-war Years*, Demetra Publishing, 2008; and *Greek Light Music of the 1935–1975 Period*, Demetra Publishing, 2008).

From interacting with Dr. Peppas in preparation of this interview, his passion for science, his students, his family, and life in general clearly shines through. We would like to congratulate Dr. Peppas on his election to the Institute of Medicine and thank him for taking the time to answer the questions that follow.

Q *What scientific contribution(s) triggered your election to the Institute of Medicine?*

A The IOM announcement included the following citation: “For seminal contributions and visionary leadership in pharmaceutical sciences, drug and protein delivery, and biomaterials science, and for pioneering fundamental work on drug delivery that has led to numerous pharmaceutical products or devices.”

Q *What does being elected to this position mean to you?*

A I was deeply honored and humbled by the decision of IOM and the recognition they bestowed upon my research group and me. Since 1976, and for almost 33 years, we have dedicated our research work to providing better treatment for our patients and to improving their quality of life. In the past 22 years, we have concentrated on finding improved treatments for diabetes, osteoporosis, and multiple sclerosis and designing or synthesizing better biomaterials for artificial organs and drug delivery products. It is so rewarding to hear that we have succeeded even a little.

Q *What do you regard as the most significant achievement of your career so far?*

A I believe my most significant achievement has been my contribution to the education of the younger generations of chemical engineers, biomedical engineers, pharmaceutical scientists, and especially industrial and academic leaders in drug delivery, controlled release, biomaterials, and nanobiotechnology. More than 650 students, indeed research collaborators, have passed through our laboratories over the past 33 years. They included 190 graduate students and postdocs. I am proud especially of the 81 Ph.D. students who have graduated from our group. Many of them are industrial leaders of the field now, and 36 of them are professors in universities. I am particularly proud that none of them has been denied tenure.

Q *Could you briefly describe the role of controlled release in your work, with an emphasis on the oral insulin delivery system you have patented, biogels used in wound healing, etc.?*

A I was educated at MIT in the early 1970s, with a strong background in mathematical analysis and physical understanding of processes. My apprenticeship next to biomedical pioneers Ed Merrill and Clark Colton led to a deep understanding of transport processes in the medical science but also to a complete appreciation of medical applications. This was done in the 1970s, at a time that other engineering schools were looking at applied research as very inappropriate for scholarly activities.... However, at MIT, cross-fertilization was extremely important in those days....



The Peppas family: Lisa, Alexi, Katia, and Nicholas. (Photo by Dr. Jack Hart, BME University of Texas)

Bob Langer, Mike Sefton (University of Toronto), and I were classmates at MIT. Mike Sefton and I did our doctorates with Ed Merrill, as did Clark Colton. Later, I served as a postdoc with Colton, while Bob Langer did his Ph.D. with him. David Tirrell (now of CalTech and a member of NAE and NAS) was an undergraduate assistant in our lab, while Pat Wong, who just retired as a VP of ALZA, was a postdoc in the same laboratory. In addition to engineering and science courses, we were taking medical courses at Harvard; these were the pre-HST days.... However, this biomedical, yet also fundamental, education of those days paid off.

Therefore, once I started as an independent researcher in 1976, it was only natural for me to set the fundamentals and rational design of drug delivery systems, biomedical devices, and biomaterials processes, such as protein absorption. In those early days, drug delivery was an empirical field where the selection of components for successful formulations was based on a heuristic approach. We started by setting up the theories and equations that led to the design of a wide range of new systems. For example, using biomedical engineering principles and new biomedical transport theories, we developed the equations that describe Fickian and non-Fickian diffusional release from controlled release devices—what researchers now call the “Korsmeyer-Peppas equation,” which has become the standard method of analysis of many pharmaceutical formulations. Using the modeling similarities of phase erosion and state erosion, we developed unified models for a wide range of drug delivery systems. Similarly, we developed the theoretical framework for the analysis of drug and protein transport through crosslinked hydrogels and biomaterials (the Peppas-Reinhart theory), ionic hydrogels

(the Brannon-Peppas theory), as well as the fundamentals of mucoadhesion/bioadhesion in gel-tissue interactions via tethers (the Huang-Peppas theory and the Sahlin-Peppas equation). The result of these studies was also the development of a number of oral drug delivery products, notably for theophylline, diltiazem, oxprenolol, and proxyphylline delivery. And, in drug and protein transport and absorption we were working on what are basically advanced solute transport models in the arterial and intestinal walls as early as 1977, long before the popular BCS system was developed.

Q *How do you anticipate the delivery system you are using to deliver insulin will impact the oral delivery of other proteins?*

A We are cautiously optimistic that the improved carriers based on complexation hydrogels that we use for protein delivery will improve the methods of oral and in general transmucosal delivery. Our studies of insulin transport using poly(methacrylic acid)/poly(ethylene glycol) complexes in contact with Caco2 and HT29-MTX cell lines indicate an improved transport from the apical to the basolateral side, while the insulin transport is 5 to 10 times higher. Animal studies have been very promising. We have now several generations of intelligent mucoadhesive, complexing hydrogels that have been used for a number of proteins, from insulin to calcitonin and growth hormone to interferon- β . But, additional studies are always needed, and our industrial partners are always asking for improved bioavailability.

Q *In what area do you think the next scientific breakthrough will occur? What will the role of controlled release be?*

A There will be several areas of major expansion of drug delivery. Some of them are already here: gene therapy, targeted delivery, and improved polymer therapeutics. But, I think the major breakthroughs will come from advanced use of intelligent materials, hybrids, and nanotechnology. Often I have read comments by the “experts” that nanotechnology and intelligent behavior are “buzz words” that mean nothing and are there only for funding purposes. Such statements, frankly such editorials, leave me cold, as they show a total lack of understanding of the fundamentals of drug delivery. The major breakthroughs in therapy, in disease treatment, and in liberation of our patients will come when new miniature devices will be equipped with advanced systems that can diagnose, detect, and deliver drugs for the treatment of patients without the patients’ active participation in the process. Some of these advances in feedback control are happening already from researchers like Frank Doyle of UC Santa Barbara, Angie Belcher of MIT, Karen Wooley of Washington University, Mariko Morishita of Hoshi University, and Maria Vicent of Valencia, scientists who do not usually come to CRS meetings.

Q *Could you recommend a publication or two from your lab that would be particularly noteworthy for our CRS readers to read?*

A My most cited publications are those that set the foundations of the field, the early work with Richard Korsmeyer, Phil

Ritger, Steve Lustig, and Lisa Brannon, as well as the pioneering work we did with Pierre Buri and Robert Gurny of the University of Geneva, Dominique Duchene and Patrick Couvreur of the University Paris-Sud, and Paolo Colombo, Ubaldo Conte, and Ruggero Bettini of the Universities of Pavia and Parma. These were heroic days that established some of the tools we use now in the field. It is impossible for me to identify just two or three papers, so I will just name some of the *most important recent work* we have published.

- The paper “Microfabrication of Intelligent Biomimetic Networks for Recognition of D-Glucose,” *Chem. Mater.* 18:5869-5875 (2006), by Zach Hilt, Mark Byrne, and me, sets the basis for the new generation of recognitive/responsive gels for diagnosis/recognition and delivery.
- The work on “Wheat Germ Agglutinin Functionalized Complexation Hydrogels for Oral Insulin Delivery,” *Biomacromolecules* 9:1293-1298 (2008), by Kristy Wood, Greg Stone, and me, is an elegant development of an advanced carrier for protein delivery.
- Finally, the work by Terry Farmer, Tom Edgar (two control engineers), and me on “The Future of Open and Closed-Loop Insulin Delivery for Diabetes Mellitus,” *J. Pharm. Pharmacol.* 60:1-13 (2008), points to the future of advanced design of insulin delivery systems.

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

A Both of my parents were educated in economics and classics and taught me from a young age to appreciate classical education but also discovery and invention. I was always fascinated by early inventions of the pioneers in engineering. At the same time I was fascinated by medicine, but I did not want to practice. My family had several generations of professors in chemistry, plant physiology, history, and archaeology, going back to Göttingen, Heidelberg, and Königsberg (my maternal family side was originally German). So, I was expected to continue a family tradition by becoming an academic. I was lucky then to find myself in Boston in the early 1970s, with exciting teachers such as Ed Merrill, Clark Colton, Alan Michaels (later of ALZA fame), Sam Bodman (recently secretary of energy in the Bush administration), and Paul Flory (who was visiting MIT for a year). It was only natural to take the academic route, as I was excited about applying my knowledge to the solution of important medical problems.

Q *What key changes have you witnessed in the collaboration between academia and industry in recent years? In your opinion, where is this collaboration ultimately heading?*

A Major changes in federal and state funding, along with the need to reach out to the public and engage in activities that will solve societal problems, have led to increased interaction and collaboration between industry and academia.... It is a major change in the way we work. I support it, and I actively interact with a number of companies, including companies I founded myself or with my students. But, I am also very apprehensive and concerned with the developing trend of almost complete academic dependence on industry....

Q *You have been a leader within the Controlled Release Society for many years, serving as President from 1987 to 1988 and providing key leadership in organizing meetings and societies throughout the world. Based on this experience and your research, what is your perspective on the field of controlled release? Are we on schedule with the visions you had for the field 20 years ago?*

A I became a member of CRS 30 years ago, and along with Robert Gurny, I ran the first international CRS meeting in Geneva, Switzerland, 24 year ago, in 1985. Our funding was miniscule with respect to what we would spend now for a meeting. My whole 1985 budget for invited speakers was \$3,000, yet we invited 30 speakers that year. We set a goal to make CRS the premier international organization in drug delivery (yes, the term was used in 1985!). Don't forget that the CRS has started in Akron, OH, by Nate Cardarelli 12 years earlier, in 1973, as a predominantly veterinary and agricultural controlled release organization. The changes proposed in the early 1980s were dramatic.... Scientifically, those were the days of better carriers, improved polymers, better processing techniques, and achievement of the Holy Grail of the field—the famous *zero-order release*. Yet, by the second international meeting of 1988 in Basel, Switzerland, the year I was CRS president, we had embarked on an ambitious program to attract biochemists, biologists, clinicians, etc. In the early 1990s we also started about 12 international CRS Chapters. Later, the arrival of other visionary leaders such as Vince Lee and the much missed Joe Robinson pushed the field toward more biological and medical sciences. Twenty years later, I think we have achieved the goals...but now we have started wondering (and rightly so) what *controlled release* truly means and if drug delivery will not be a better title.

Q *Your hobbies include a love of history and opera, in which you are well published. How have you been able to balance these “hobbies” with your scientific career? More generally, how do you balance work and family life?*

A My wife and I have a wonderful family life. We are the parents of Katia (Katherine), an 8-year old, and Alexi (Alexander), a 5-year old, and children come first in our life no matter what. This is in fact the reason why we do not come to CRS meetings as often any more. We can both afford to have a balanced life without interfering with our jobs. Lisa (who was very active in CRS in the 1990s and was in fact treasurer of the Society from 1995 to 1998) is vice president of Appian here in Austin. Beyond that, my life has never been just chemical engineering and controlled release. Music and history have been an integral part of my life. Opera is very dear to my heart (I studied voice in the Hellenic Conservatory of Music in Athens while in high school and college, although I never finished my studies), and I have spent 40 years writing about Italian, French, and German opera. For me this is my true love and what makes me relax when research gets too demanding.

Q *What personal traits have best suited you in advancing your career to the point it is currently at?*

A Perseverance, hard work, and dedication to my life goals. I do not give up easily...and as both Bob Langer and I have noted in the past, the early days of drug delivery were not easy for us engineers.... How many colleagues questioned what a Ch.E. was doing in drug delivery.... Engineers were not supposed to work in such...a mundane field.... Yet now, “drug delivery” is a main field of research for chemical engineers!

Q *Has working at Purdue University and the University of Texas at Austin made you into a college football fan? If so, in a championship game would you rather have Drew Brees or Vince Young on your team?*

A I have never attended a football game.... Saturday afternoon games always competed with something else, you know...the Met broadcasts! But I have watched both quarterbacks after they became professionals. Clearly Vince was better as a college player, but Drew Brees is regal now.... Both ways Austin wins....Drew Brees was from Westlake High school in Austin, TX!

Bibliography

Laboratory of Biomaterials, Drug Delivery, Bionanotechnology and Molecular Recognition website at University of Texas at Austin (www.che.utexas.edu/research/biomat/index.htm).

Institute of Medicine website and press release (www.iom.edu/CMS/59070.aspx). ■

Welcome New Members

Maria Antonieta

Annunziato

Shruti U. Bhat

Waubalem Birmachu

Atef Boulos

Yan Chen

Michael Danquah

James C. Dinunzio

Yildiz Erginer

Sophie Hughes

Jes Kristian Jacobsen

Mayank R. Joshi

David G. Lessard

Zhuzhu Li

Vineet Luhariwala

Amrita M. Mehta

Abeer Hashim Mohamed

Ahmed

Srinath Palakurthi

Ravikiran Panakanti

Satheesh K. Podaralla

Harry Quandt

John Rynak

Sonal Saluja

Nitin S. Satarkar

Peter M. Seiler

Rita E. Serda

Rasika Suryawanshi

Kurt E. Vagle

Mathias Walther

Hao Wu

Jin Xu

Walter P. Zackowitz

Qiuye Zhang

Rui Zhu

Mechanistic Insights into Stratum Corneum Hydration and Implications for Transcutaneous Vaccine Antigen Penetration

Grace Tan,¹ Peng Xu,¹ Vijay T. John,^{1,2} Louise B. Lawson,³ Lucia C. Freytag,³ John D. Clements,³ and Jibao He⁴

Introduction

The skin and mucosa are recognized targets for depositing vaccine antigens and are superior over conventional injection that bypasses the notable immune system of the skin. However, substantial penetration through the skin barrier, i.e. the stratum corneum, is mostly limited to small molecules (<500 Da). Penetration by large macromolecules (>500 Da) is obstructed by the dense lipid-filled channels between corneocytes. The grand challenge for transcutaneous vaccine delivery is to have the antigen penetrate just beyond the stratum corneum to reach immunologically sensitive Langerhans cells in the epidermis. Vaccine antigen taken up by Langerhans cells is then drained to the lymph node, the antigen is presented to T cells, and an immune response is elicited (1).

In order to enhance penetration through the stratum corneum, various methods to breach the stratum corneum barrier have been studied, among which include the removal of the skin barrier by skin stripping or abrasion (2) and the use of penetration enhancers (3). From a safety standpoint, abrasion that involves removal of the skin barrier is less desirable because pathogens may gain easy access to the body due to the longer turnover time period required for regrowth of the stratum corneum. Chemical penetration enhancers, on the other hand, need to be carefully selected due to irritation issues. Water is by far the safest and most natural penetration enhancer known to improve skin permeability (4). However, the effect of water on the stratum corneum is still not thoroughly understood. It is of interest, therefore, to investigate the extent of “disruption” that water can inflict upon the skin, how these disruptions occur, the application period required before such disruptions are observed, and whether the disruptions are reversible. The viability of proteins penetrating skin disrupted by hydration was examined by applying a solution containing a fluorescently tagged protein molecule (fluorescein isothiocyanate-bovine serum albumin, 68 kDa) onto the skin. The studies were performed on porcine skin, which has a lipid composition that most closely resembles human skin (5).

Results and Discussion

When a wet Band-Aid was applied onto porcine skin to mimic application of a hydration patch (Figure 1), the stratum corneum responded to hydration by first expanding keratin-filled

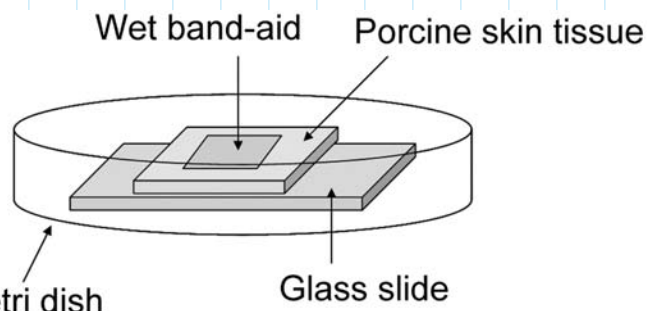


Figure 1. Illustration of porcine skin hydrated using a wet Band-Aid.

corneocytes due to the high affinity of keratin for water. This was observed when hydrated porcine skin was imaged using a cryo-field emission scanning electron microscope. A more spacious keratin network was observed inside the corneocytes as a result of the corneocytes expanding and was evidenced by an increased porosity in the corneocytes when they were sublimed (Figure 2). During this period, only a very slight increase in stratum corneum thickness occurred.

Upon a longer period of hydration of porcine skin, water-filled pockets (water pools) started to appear in the lipid region between corneocytes (Figure 3A). This was a result of the delamination of the lamellar lipid layers. It is hypothesized that swelling of the corneocytes due to hydration created bending stresses at the edges of the corneocytes, leading to weakening of these areas. As water entered into the intercorneocyte lipid region, conformation changes in lamellar lipids to form vesicular lipid structures may have occurred. This might explain why spherical shaped beads were frequently observed in the water pools occurring in highly hydrated porcine skin (Figure 3B and C). A comparison of natively hydrated porcine skin with porcine skin hydrated for 6 hr using a wet Band-Aid is shown in Figure 4.

The water pools were only observed in specific localized regions in the horizontal plane of the stratum corneum, suggesting that weaker regions of the stratum

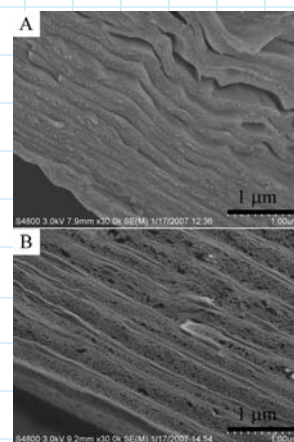


Figure 2. Cryo-SEM image showing the dense keratin network in corneocytes for (A) natively hydrated porcine skin and (B) porcine skin hydrated for 1 hr using the wet patch. A slight expansion in the thickness of the corneocytes, as well as an increase in porosity of the keratin network, is observed due to the absorption of water.

¹Department of Chemical & Biomolecular Engineering, Tulane University, New Orleans, LA, U.S.A.

²Corresponding author. Tel: +1.504.865.5883; Fax: +1.504.865.6744; E-mail: vijay.john@tulane.edu.

³Department of Microbiology & Immunology, Tulane University, New Orleans, LA, U.S.A.

⁴Coordinated Instrumentation Facility, Tulane University, New Orleans, LA, U.S.A.

corneum existed that were first breached by hydration. With prolonged hydration, the water pools increased in number, and some might eventually have merged to form a larger pool. These large water pools contributed to a substantial increase in the thickness of the stratum corneum. A mechanism for the hydration of the stratum corneum is proposed and presented in Figure 5.

The reversibility of the disruptions in hydrated porcine skin was examined by drying the skin in air before imaging. The skin resumed its compact structure with the disappearance of previously formed huge water pools in the stratum corneum (Figure 6).

The penetration of fluorescein isothiocyanate-bovine serum albumin that was similar in size to vaccine antigens through porcine skin was investigated using a confocal microscope (Figure 7). The fluorescent protein showed little to no penetration after 1 hr of application on porcine skin. However, when the skin was hydrated using the wet patch, enhanced penetration was observed, with the fluorescent protein reaching the epidermis and occasionally the dermis. The restored porcine

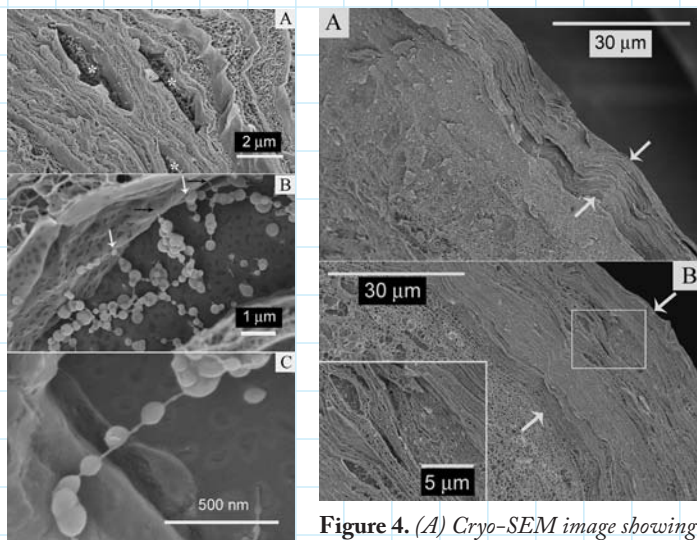


Figure 4. (A) Cryo-SEM image showing the cross-section of natively hydrated porcine skin obtained after cryo-fracturing. The stratum corneum, which runs diagonally from the top left to the bottom right in the picture, is observed overlying the viable epidermis. The stratum corneum of the untreated tissue is approximately 10 mm thick (marked by arrows) with a compact ultrastructure. (B) Stratum corneum of porcine skin hydrated for 6 hr is slightly over 30 mm thick (marked by arrows). The presence of water pools causes a substantial increase in the thickness of the stratum corneum. The inset is a higher magnification image of the boxed region and shows details of intercellular space expansion forming water pools.

Figure 3. Contents of water pools in highly hydrated porcine skin. (A) Water pools (asterisks) frequently contain particulate matter. (B) Agglomerated polydisperse spheres (or beads) attach through thin strings to form networks in a water pool. Some beads are fused to the cisternal walls (white arrows), while others attach to the cisternal walls through thin strings (black arrows). The beads may be disrupted lipids that have rearranged and formed multilamellar vesicles. (C) High-magnification image of globular structures in a water pool.

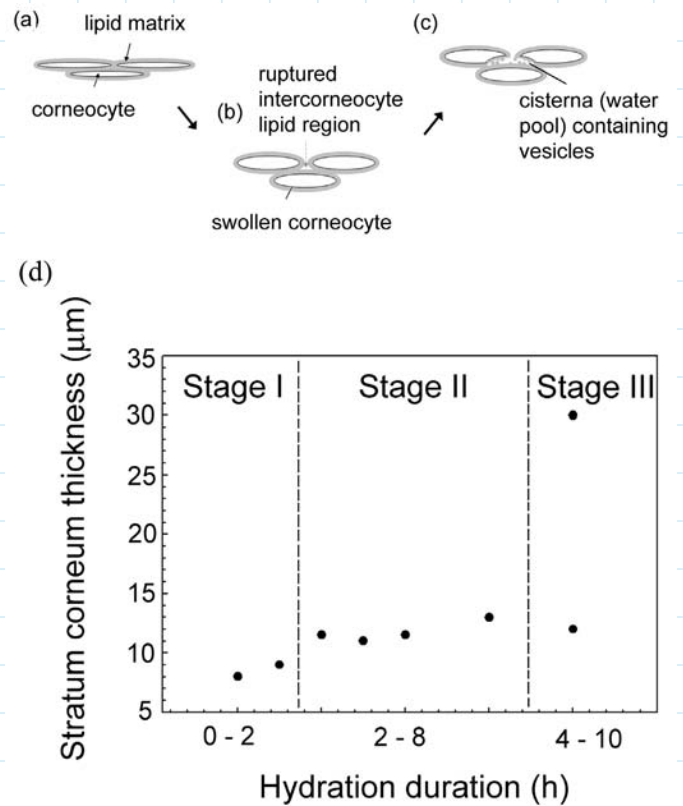


Figure 5. Illustration depicting changes in corneocytes and the intercellular lipid matrix upon prolonged external hydration. (A) Initially corneocytes were densely packed in the stratum corneum. (B) Upon external hydration, corneocytes became swollen, leading to small ruptures in the intercellular lipid matrix. (C) The ingress of water leads to the formation of a water pool containing spherical lipid aggregates. (D) Stratum corneum thickness as a function of hydration duration for a single batch of porcine skin.

skin that had dried did not show penetration of the protein through the stratum corneum.

Conclusions

The skin is a dynamic entity, and penetration pathways are highly dependent not only on initial microstructure but also on induced conformational changes.

The stratum corneum thickness with hydration time can be divided into several stages. Initially the corneocytes expand as they absorb water; bending stresses are created at the edges of corneocytes, which leads to weakening and delamination of the lamellar lipid layers. Water pools form upon delamination, and large molecule penetration through the skin barrier is possible due to modulation in lipid conformation and skin microstructure. This study shows the potential to design a

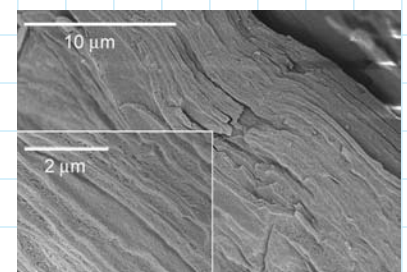


Figure 6. Restored porcine skin tissue showing absence of huge water pools and a compact ultrastructure. Inset shows a higher magnification image of the corneocytes in the restored skin.

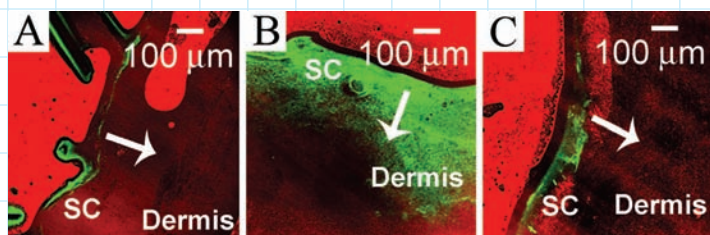


Figure 7. Penetration of FITC-BSA through (A) natively hydrated, (B) highly hydrated, and (C) restored porcine skin tissue after FITC-BSA was loaded for 1 hr.

method for antigen delivery using wet patches (hydrogels) or hydrating creams.

References

1. Glenn, GM, Scharton-Kersten, T, Alving, CR. Advances in vaccine delivery: Transcutaneous immunization, *Exp. Opin. Invest. Drugs* 8: 797-805 (1999).
2. Frerichs, DM, Ellingsworth, LR, Frech, SA, Flyer, DC, Villar, CP, Yu, J, Glenn, GM. Controlled, single-step, stratum corneum disruption as a pretreatment for immunization via a patch, *Vaccine* 26: 2782-2787 (2008).
3. Mitragotri, S. Synergistic effect of enhancers for transdermal drug delivery, *Pharm. Res.* 17: 1354-1359 (2000).
4. Robert, MS, Walker M. Water, the most natural penetration enhancer, Marcel Dekker, New York (1993).
5. Simon, GA, Maibach, HI. The pig as an experimental animal model of percutaneous permeation in man: Qualitative and quantitative observations—An overview, *Skin Pharmacol. Appl. Skin Physiol.* 13: 229-234 (2000). ■

The CRS Foundation

Established with a clear vision ...

to provide a durable source of financial support for the advancement of educational and organizational activities that enrich and extend the research and development of CR-associated technology platforms involved in the delivery of bioactives and other functional materials

... the CRS Foundation needs your help to positively impact the future.

To learn more about the CRS Foundation

Contact Deborah Woodard at
dwoodard@scisoc.org
or +1.651.994.3817.



Advertise in the CRS Newsletter



Reach your target audience of thousands of international scientists, industry leaders, academicians, and others in the controlled release and delivery community. Distributed via mail and online, the combined exposure opportunities for each issue averages more than 15,500.

For more information, contact Debby Woodard, CRS Business Development, at dwoodard@scisoc.org or +1.651.994.3817.

Raman Microscopy Imaging of Nanocarrier Systems for Cellular Uptake and Trafficking

Christian Matthäus,^{1,2} Tatyana Chernenko,¹ Lara Milane,³ Amit Kale,³ Luis Quintero,⁴
Mansoor Amiji,⁴ Vladimir Torchilin,³ and Max Diem¹

Introduction

New discoveries in cell biology are often associated with the development of new microscopy techniques, which allow visualization of subcellular processes and the structural organization of cellular organelles. Over the past 20 years several techniques have been introduced that employ continuous or pulsed laser light to stimulate molecular excitations. Examples include confocal fluorescence microscopy, two photon microscopy (TPM), and second and third harmonic generation imaging (SHGI and THGI, respectively). The first two examples are based on electronic transitions, whereas the latter two are based on light scattering. Raman microscopy utilizes inelastic light-scattering effects that excite molecular vibrations and is, therefore, a combination of vibrational spectroscopy and optical imaging. It has the intrinsic advantage of providing information about molecular compositions and structures directly, without introducing external labels or dyes. At present, Raman microscopy is commonly used to image drug distribution patterns in coatings of cardiovascular stent implants and aerosol particles for pulmonary drug delivery (1).

Of particular interest are uptake efficiency, cellular transport, drug release, and the fate of nano-sized delivery systems upon administration *in vitro* and *in vivo*. The chemical composition and molecular structure of nanoparticles is variable and complex, ranging from amphiphilic molecules that assemble into micelles or liposomes to nano-structures of biodegradable polymers (2). Often the surfaces of the particles are modified with cell-penetrating peptides, such as HIV-1 trans-activating transcriptional activator-derived (TAT) peptide, or antibodies to enhance cellular uptake and organelle-specific delivery. Certainly, any microscopy technique that can monitor uptake and distribution of these particles offers great insight into their intracellular distribution and metabolism. So far two approaches have been utilized to image nanoparticles in individual cells (3). It is possible to fluorescently label the drug/payload molecule or the nanocarrier and use fluorescence microscopy to study uptake and cellular distribution. Another option is to incorporate colloidal gold particles, which can be visualized under an electron microscope. However, both techniques have disadvantages. Fluorescence microscopy often suffers from fast photo bleaching and low specificity because of strong

backgrounds. Furthermore, introducing fluorescent labels can alter the biological behavior of the payload or particle of interest. The second approach monitors the carrier system only indirectly. Neither technique provides significant insight into the kinetics of drug release from a nanocarrier platform. We believe that Raman microscopy is a valuable complement to common microscopic techniques, as it may provide spectroscopic information about chemical changes associated with cellular metabolism.

Results and Discussion

Using liposomes, micelles, and polymeric nanoparticle delivery systems, we have been investigating the use of Raman microscopy for intracellular delivery and trafficking. Figure 1 shows two Raman images along with a microscopic picture of a MCF-7 cell incubated with liposomes at a concentration of 2 mg/mL for 12 hr. All images presented here were recorded using a WITec (Ulm, Germany) Raman microscope, using a 488 nm excitation source and a water immersion objective (60×/NA = 1.00). In order to distinguish the phospholipids of the liposomes from naturally occurring phospholipids or lipids inside the cytoplasm, the liposomes were assembled using perdeuterated 1,2-distearoyl- d_{70} -sn-glycero-3-phosphocholine (DSPC- d_{70}), where the hydrogens of the aliphatic side chains had been replaced by deuterium. It should be mentioned that the incorporation of isotopes did not affect the chemical properties of the molecules. Figure 1B was constructed from the scattering intensities of the C-H stretching vibrations between 2,800 and 3,050 cm^{-1} . The image is non-specific with respect to the chemical composition of the different areas within the cytoplasm and simply reflects differences in density. Figure 1C was obtained using a mathematical algorithm commonly known as vertex

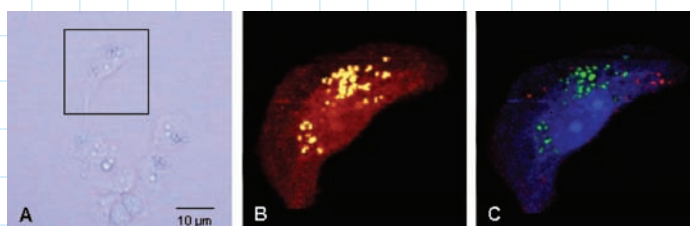


Figure 1. (A) Microscopic bright field and Raman images of a MCF-7 cell incubated with DSPC- d_{70} liposomes. (B) Image reconstructed from scattering intensities associated with stretching vibrations of C-H bonds. (C) Image generated by a spectral unmixing algorithm based on vertex component analysis (VCA). The red regions in C show the distribution of DSPC- d_{70} liposomes.

¹Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA, U.S.A.

²Corresponding author. Tel: +1.617.373.7698; Fax: +1.617.373.7773; E-mail: c.matthaeus@yahoo.de.

³Department of Pharmaceutical Sciences and Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston, MA, U.S.A.

⁴Department of Engineering, University of Puerto Rico, Mayagües, Puerto Rico.

component analysis (VCA), which decomposes the spectra in a given dataset into linear combinations of the most dissimilar spectra (4). The associated spectra are plotted in Figure 2. Spectrum 2A resembles a typical protein spectrum. All spectral features can be assigned to vibrational motions of the protein backbones and their residues. By plotting the abundances of the blue spectra, the cell body can easily be reconstructed. The red regions reflect the distribution of the liposomes. The associated spectrum plotted in 2C shows very clearly the scattering intensities resulting from the C-D stretching vibrations between 2,000 and 2,300 cm^{-1} . The green droplet-like structures were high in lipid content, as can be identified by their spectral features, and were likely to be transport vesicles. After 12 hr of incubation, a significant amount of liposomes had been incorporated into the cytoplasm. Usually, liposomes are taken up by endocytotic pathways, which can lead to aggregation on the micrometer scale. For non-modified liposomes, we found that after 12 hr of incubation the uptake resulted in saturation. Longer incubation times did not increase the amount of liposomes inside the cells. However, over time translocation from the cell peripheries toward the perinuclear region could be observed (5).

The uptake of liposomes can be significantly enhanced by introducing cell-penetrating peptides into the liposome

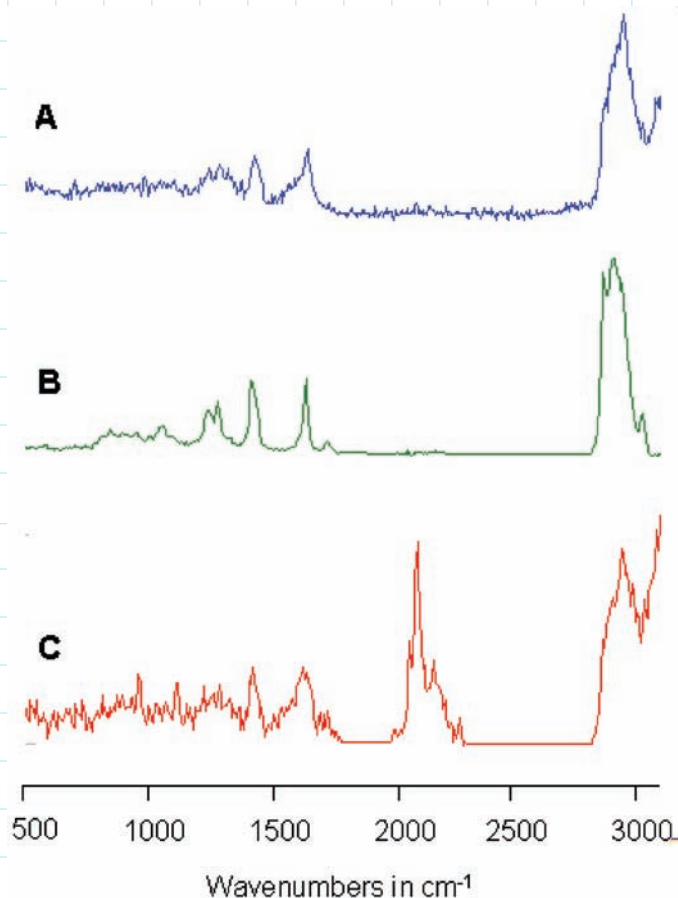


Figure 2. Raman spectra associated with the image generated by the VCA algorithm in Figure 1C. The abundance of spectra within the dataset are shown in corresponding colors in Figure 1C.

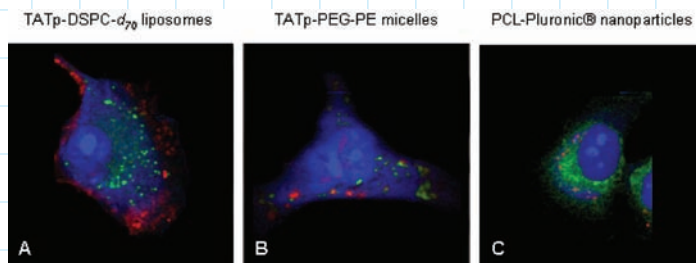


Figure 3. Raman images of cells incubated with different types of drug delivery systems. (A) A MCF-7 cell treated with TATp-modified DSPC- d_{70} liposomes; (B) a HeLa cell inoculated with a TATp-PEG-PE micelle system; and (C) a HeLa cell exposed to PCL-Pluronic[®]-based nanoparticles. The intracellular distribution of the carrier systems are shown in red for all three images. The blue regions of each cell correspond to the cytoplasm and nucleus (nucleolus lighter blue,) while the green regions are most likely high lipid-content vesicles (A and B), the endoplasmic reticulum (A and C), and mitochondria (C).

membrane. Figure 3A shows the Raman image of a cell incubated with TATp-modified liposomes for 3 hr. Not only was the amount of liposomes that penetrated into the cells drastically enhanced, the uptake kinetics also were accelerated by at least a factor of two. Saturation was reached after 6 hr of incubation.

Along with the image of the cell treated with TATp-DSPC- d_{70} , two other cells are shown that were incubated with two different types of delivery systems. The cell in Figure 3B was incubated with TATp-modified PEG-PE micelles for 8 hr. Figure 3C shows a cell exposed to non-modified poly(ϵ -caprolactone) (PCL)-Pluronic[®] nanoparticles for 7 hr. For both systems, the spectral features of the nanoparticle components were sufficiently different from the spectral features of the naturally occurring cell components, so labeling with deuterium was not essential. However, labeling with deuterium enhanced the sensitivity because of minimal or no spectral overlay. In principle, any organic molecule can be labeled with deuterium, which will be especially interesting for studies investigating the intracellular release of pharmacologically active compounds from nanocarrier systems. Raman microscopy could prove to be an invaluable tool in the field of drug delivery.

References

1. Belu, A, Mahoney, C, Wormuth, K. Chemical imaging of drug eluting coatings: Combining surface analysis and confocal Raman microscopy, *J. Control. Release* 126: 111-121 (2008).
2. Torchilin, V, ed. *Nanoparticulates as Drug Carriers*, Imperial College Press, London (2006).
3. Maysinger, D, Lovrić, J, Eisenberg, A, Savić, R. Fate of micelles and quantum dots in cells, *Eur. J. Pharm. Biopharm.* 65: 270-281 (2007).
4. Nascimento, J, Bioucas Dias, JM. Vertex component analysis: A fast algorithm to unmix hyperspectral data, *IEEE Trans Geosci. Remote. Sens.* 43: 898-910 (2005).
5. Matthäus, C, Kale, A, Chernenko, T, Torchilin, V, Diem, M. New ways of imaging uptake and intracellular fate of liposomal drug carrier systems inside individual cells, based on Raman microscopy, *Mol. Pharm.* 5: 287-293 (2008). ■

MICROBES in a Mug

Research Competition

With its finger ever on the pulse of cutting-edge scientific advancement, the UKICRS committee has scoured the globe (well, the back issues of the *Journal of Medicinal Chemistry*, to be exact) in a bid to bring you the ultimate in competitions. Not content with having you waste time with cryptic crosswords and super sudokus, we invite you to join us in amassing an elite scientific army willing to ask the questions that cause mere mortals to pursue degrees in “Retail Floristry” or “Golf & Sports Turf Management” (for real! see www.bspcn.com/2007/10/19/top-10-most-unusual-college-degrees/).

Interesting Fact No. 1: Researchers in Slovenia have recently reported that the catechin molecules in green tea have potent antimicrobial properties, inhibiting the essential bacterial enzyme DNA gyrase. (J. Med. Chem. 50: 264–271 (2007); 10.1021/jm060817o).

Interesting Fact No. 2: Leave a used coffee cup on your office desk for a couple of weeks and a “bacterial oasis” worthy of gold medal at the RHS Chelsea Flower Show will effortlessly bloom into existence.

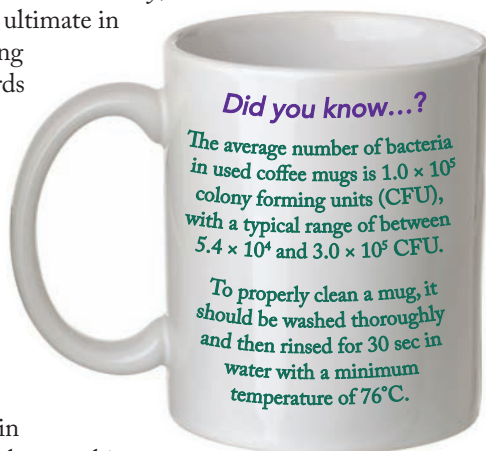
But, what about tea cups? Specifically, what about used cups of green tea—do all those catechins left in the dregs of the cup in-

hibit bacterial growth compared to used coffee cups? Does the presence of milk in coffee affect the extent of bacterial growth?

And so, your mission is to provide UKICRS with photographic evidence in a bid to answer these (and related) questions.

Brief details of your experimental methods and results, and accompanying photographs, should be e-mailed to ukicrs@gmail.com. The winner will be announced at the UKICRS 2009 Symposium, and a selection of the best results will be published in the 2009 newsletter and on the UKICRS website. If the response is overwhelming, we’ll even draft an article for submission to the *Annals of Improbable Research* (www.improbable.com/).

Most bacteria collected in your coffee or tea cup will not be harmful. However, once they multiply into millions of colonies, they can become a hazard. So, here’s our handy tips for keeping safe: don’t keep the mugs too close to where you normally sit; don’t expose open cuts to the bacteria; don’t ingest or breathe in the growing bacteria; after a few weeks of growth, cover your mug with a clear Petri dish lid until your culture is complete; and afterward, safely destroy the fuzzy fields with bleach. Of course, UKICRS accepts absolutely no liability for any infection, injury, or death resulting from all this micro mayhem! ■



Back in Europe

Ijeoma F. Uchegbu

CRS Scientific Secretary, University of London, U.K.



CRS is back in Europe July 18–22, 2009! Our Annual Meeting & Exposition that is, and what an Annual Meeting & Exposition it promises to be. Your Programme Chairs Paolo Ferruti, Paul Gellert, and Tamara Minko; C&DP Programme Chairs Claudio Ortiz and Birgit Schleichbaum; and Veterinary/Animal Health Programme Chairs Raid Alany and Cyril Desevaux have done a sterling job on your behalf and assembled an absolutely stupendous programme. We have

some really experienced and eminent plenary speakers booked who are looking forward to sharing their knowledge and experience with you. On general issues affecting the health of the world and its peoples, we have two notable speakers: Nobel Laureate R. K. Pachauri of the United Nations Intergovernmental Panel on Climate Change and Silvio Grattini of the Mario Negri Institute for Pharmacological Research. In keeping with the health theme, Robert Kiss of the Belgian National Fund for Scientific Research will be speaking on the deadly disease that is cancer, and metastasis in particular. Delivering bioactives in an effort to combat disease will be a core feature of our meeting, and two plenary speakers will kick this off, namely Alan Hoffman of the University of Washington, who will speak on drug delivery in general, and Gary Cleary of Corium International, who will share his knowledge on delivering drugs via the skin. Finally, in a neat roundup and in an effort to close the loop, Heico Frima of the European



Photo by Cees van Roeden, courtesy of Wonderful Copenhagen.

Commission will speak on the funding landscape according to the European Commission.

There will be a number of mini-symposia covering health topics such as malaria, AIDS, and neurodegeneration and a special session on how to translate research ideas into real treatments for real patients. To make the meeting a little more interactive, we also have two new events this year: roundtable discussions in the areas of nanomedicines and tablet manufacture. These two events will comprise small groups and focus on discussion rather than lectures. Make sure you sign up as space will be limited!

There will be ample opportunities to hear from our valued contributors about their latest work, either via an oral presentation at any one of a number of sessions on oral drug delivery, nanotechnology, microencapsulation, protein delivery, and much more, or as part of the poster presentations. There will be the same buzz around the posters as we had in New York, which were so well attended.

This leads me to encourage you to make sure you are in Copenhagen to find out who is doing what and how; to share your work with your peers; and to meet up with old friends, make new friends, and grow your research or business. Get that order for new business cards done, as there will be a whole lot of swapping going on in the busy exposition and poster hall!

Finally a word about Copenhagen. Copenhagen is a beautiful city with a stunning waterfront and wonderful architecture—sorry to be going on about it so much, but it really is a great place to visit.

See you in Copenhagen! ■



Photo by Cees van Roeden, courtesy of Wonderful Copenhagen.

Registration Form

Controlled Release Society • 36th Annual Meeting & Exposition
July 18-22, 2009 • Bella Center • Copenhagen, Denmark

Register online at <http://controlledreleasesociety.org/meeting>

Advance Registration Deadline—May 4, 2009

Complete the following information. Please print clearly to ensure correct spelling on name badge.

Information below is New Address Alternate Address

Registrant is Male Female

Mr. Mrs. Ms. Dr. Professor

First Name _____ Middle Initial _____

Last/Surname _____

Name Preferred on Badge (first name only) _____

Job Title _____

Date of Birth (new members only) _____
Month Day Year

Information below is New Address Alternate Address

Employer/Company/Institution _____

Company Address _____
Street

_____ *City State/Province*

_____ *Zip/Postal Code Country*

Daytime Telephone _____

Facsimile _____

E-mail _____

Primary Track of Interest

- Veterinary
- Consumer & Diversified Products
- Bioactive Materials

Work Category

- Academic
- Government
- Industry
- Media
- Other _____

Volunteer Opportunities

- Please send information on volunteer opportunities.

Special Accommodations

- Check here if you require special meals or accommodations to fully participate in this meeting. Please be specific:

Mailings

- Do NOT include my information in rented mailing lists.
- Do NOT include my information in membership directories.

Cancellation/Refund Policy

Registration cancellations must be made in writing and be received by CRS no later than May 25, 2009. Cancellations received by this date are subject to a \$100 processing fee; ticketed events will be fully refunded. Registration and ticketed event cancellations received after May 25, 2009, are NOT subject to a refund.

Register by any of these methods

Internet:

www.controlledreleasesociety.org/meeting

Fax: +1.651.454.0766

(Faxed forms must include credit card information to be processed)

Mail: CRS Meeting Registration
3340 Pilot Knob Rd
St. Paul, MN 55121 U.S.A.
Phone: +1.651.454.7250

Must complete reverse side to register.

Registration Fees

Registrations postmarked or faxed by date listed will be charged appropriate fee.

Registration Classifications*	Early By May 4, 2009	Regular/Onsite After May 4, 2009	Amount
Member	\$785	\$985	_____
Student/Post-doc Member	\$255	\$345	_____
<i>Meeting + Membership</i>			
Registration + Regular Membership	\$928	\$1,128	_____
Registration + Student/Post-doc Membership	\$289	\$379	_____
Nonmember	\$975	\$1,175	_____
Student Post-doc Nonmember**	\$330	\$420	_____
Exhibitor***	\$725	\$925	_____
Sunday Full Day	\$700	\$750	_____
Single Day	\$625	\$675	_____

Monday Tuesday Wednesday

Educational Workshop—Select One

One-day Workshop (July 18, 2009)

1. RNA Interference Biology and Therapeutics

Regular	\$485	\$585	_____
Student/Post-doc	\$185	\$235	_____

Two-day Workshops (July 18 and 19, 2009)

2. Imaging in Drug Development
3. *In Vivo* Dissolution—Is It a Reality? Can It Be Correlated to *In Vitro* or *In Silico* Dissolution?
4. Micro and Nano Encapsulation

Regular	\$630	\$730	_____
Student/Post-doc	\$235	\$285	_____
Regular	\$630	\$730	_____
Student/Post-doc	\$235	\$285	_____
Regular	\$630	\$730	_____
Student/Post-doc	\$235	\$285	_____

Young Scientist Events—Free to students, post-docs, and/or scientists under 40 years of age or new to the area of controlled release within the past 5 years.

5. Saturday Young Scientists Workshop
6. Sunday Young Scientists Workshop
7. Tuesday Young Scientists Get Up; Get Educated!
8. Wednesday Young Scientists Get Up; Get Educated!

Additional Tickets

	Quantity	Amount
9. Extra Opening Reception Ticket	_____	\$75
10. Closing Reception/Banquet - Beef Entree	_____	\$170
11. Closing Reception/Banquet - Vegetarian Entree	_____	\$170
12. Additional <i>Transactions</i> CD (one CD included with registration)	_____	\$115

Travel Grant Contribution

Contribution to support graduate student travel for meeting.
Contributions of \$25 or more receive print acknowledgments.

Contribution _____

Joseph R. Robinson Scholarship Fund

Contribution to help support a graduate student studying the science of delivery of bioactives.
Donations of \$100 or more receive print acknowledgments.

Contribution _____

Total _____

* **Member/Nonmember/Student or Post-doc Member or Nonmember/Meeting + Membership/Exhibitor** fees include the Tablet Manufacturing Roundtable, Releasing Technology Workshops, Soapbox Sessions, Nanomedicines Roundtable, Young Scientist events, State-of-the-Industry Session, Partnering Sessions, Pearls of Wisdom Sessions, Highlights of Student Posters Session, First Timers'/Members' Meeting, Opening Exposition and Reception, Exposition, Podium and Poster Scientific Sessions, and one complimentary copy of the *Transactions* CD. Tickets must be purchased for an educational workshop and for the Closing Reception/Banquet (\$170). Student or Post-doc Nonmembers and Exhibitors must register by fax or mail.

Sunday Full Day fee includes the Tablet Manufacturing Roundtable, Young Scientist Workshop, Releasing Technology Workshops, Soapbox Sessions, Nanomedicines Roundtable, Young Scientist Roundtable, State-of-the-Industry Session, Partnering Sessions, Pearls of Wisdom Sessions, Highlights of Student Posters Session, First Timers'/Members' Meeting, Opening Exposition and Reception, and one complimentary copy of the *Transactions* CD. Sunday Full Day registrants must register by fax or mail.

Single Day (Monday/Tuesday/Wednesday) fee includes access to the Scientific Sessions and Exposition and a complimentary copy of the *Transactions* CD. Tickets must be purchased for the Closing Reception/Banquet (\$170).

Educational Workshop fee includes a notebook, lunch on Saturday, and morning and afternoon breaks.

** Student or Post-doc Nonmembers must have a faculty member sign to qualify for the Student or Post-doc Nonmember rate.

Advisor Name

Advisor E-mail

*** Each exhibiting company is entitled to a specified number of complimentary annual meeting registrations. See the exhibit details on the website for more information.

Payment Information

Check enclosed, payable to CRS (U.S. funds only drawn from a U.S. bank)

Charge: VISA American Express MasterCard

Card No. _____

Expiration Date ____/____/____

Cardholder Name (please print) _____

Cardholder Signature _____

See These Exhibitors at the 36th CRS Annual Meeting & Exposition

July 18–22, 2009 • Copenhagen, Denmark

Exhibiting companies that have reserved space at the 36th Annual Meeting & Exposition of the Controlled Release Society, as of press time, are listed below. For ongoing updates, visit www.controlledreleasesociety.org/meeting/exhibitors/currentExhibitors.cfm.

3M Drug Delivery Systems
ADD Technologies Ltd
Alkermes
Asahi Kasei Chemicals Corp.
Avanti Polar Lipids, Inc
Aveva Drug Delivery Systems
Azopharma Product Development Group
Banner Pharmacaps
BASF Corporation
Bio-Images Research Ltd
Biovail Contract Research
Boehringer Ingelheim
Brabender GmbH
Brookwood Pharmaceuticals
Buchi Corp
Caleva Process Solutions
Camurus AB
Capsulation Pharma AG
Catalent
CMA/Microdialysis
Colorcon, Inc.
Drug Delivery Technology
DSM Biomedical
Duoject Medical Systems Inc.
DURECT Corp.

Elan Drug Technologies
Elsevier
Erweka GmbH
Eurand, Inc.
Evonik Industries
FMC Corporation
Gaylord Chemical Company
Genzyme Pharmaceuticals
Halozyme Therapeutics
Hanson Research Corporation
Henkel
Hisamitsu Pharmaceutical Co., Inc.
Informa Pharmaceutical Science
LifeCycle Pharma A/S
Lipoid AG
Logan Instruments Corp.
LTS Lohmann Therapy Systems
Lubrizol Advanced Materials, Inc.
Microfluidics
Micro-Sphere S.A.
Molecular Profiles
Mylan Technologies Inc.
Nisco Engineering AG
NOF Europe
Northern Lipids Inc
Noven Pharmaceuticals, Inc.

Novozymes
OctoPlus NV
O'Hara Technologies
Oxford Instruments
PharmaForm
Pharmatek Laboratories
Pierre Fabre Medicament
PII
Polymun Scientific GmbH
PURAC Biomaterials
Rohm & Haas
Scintipharma Inc
Shin-Etsu Chemical Co., Ltd.
Simulations Plus Inc
Soliqs
SOTAX AG
Southwest Research Institute
Stable Micro Systems
Surface Measurement Systems Ltd
SurModics
Technology Catalysts
Thermo Scientific
Varian, Inc.
Vector Corporation
Wyatt Technology Europe GmbH
XSpray Microparticles

Questions?

Contact Debby Woodard, CRS Business Development
+1.651.994.3817 • dwoodard@scisoc.org



2009 Membership Renewal Form

CRS membership is based on the calendar year: January 1 – December 31.
Dues must be paid in full by February 28, 2009, to be eligible to vote in the spring 2009 election.

Personal Data

Have you previously been a member of CRS? Yes No

The address listed is: Business Home

Check the appropriate box: Mr. Mrs. Ms. Dr.

Name _____
First M.I. Last

Title _____

Degree _____

Company/Institution _____

Address _____

City _____

State/Province _____

Zip/Postal Code _____

Country _____

Telephone _____

Fax _____

E-mail _____

Note: The information you provide us below will remain confidential.

Date of Birth / / Gender: Male Female
Month Day Year

Select a category that best describes your work:

Academia Industry Government Student

Other _____

Primary track of interest:

Bioactive Materials Consumer & Diversified Products Veterinary

How many years in this field? _____

I prefer to receive CRS Newsletter/communications by: (check one)

E-mail Direct Mail

E-mail preference: HTML Text

I want to receive information regarding Young Scientist programs

Do not include my information in rented mailing lists

Do not include my information in membership directories

Current Memberships

Please indicate the associations of which you are already a member:

AAAS FIP RSC

AAPS JSDDS Other _____

ACS PDA _____

* Student Status Verification

I attest that the named individual is a full-time, degree-seeking student.

X _____
Signature of advisor or department chair

Printed Name _____

Expected Graduation Date _____

Telephone _____

E-mail _____

Membership Dues

Paid membership includes a complimentary subscription to the CRS Newsletter and one copy of the 36th Annual Meeting Transactions CD.

Individual \$143

Student/Post-Doc* \$34

* Please complete the student verification at the bottom of the previous column

Subtotal Membership Dues \$ _____

Journal Subscriptions (check one or more)

Must be a current individual or student member.

Journal of Controlled Release (Vol. 133 – 140)
 Official Journal of CRS – Print \$150

Journal of Controlled Release (Vol. 133 – 140)
 Official Journal of CRS – Online \$120

European Journal of Pharmaceutics and Biopharmaceutics
 (Vol. 71 – 73, 9 issues) \$120

Biomaterials (Vol. 30, 36 issues) \$325
 Includes ScienceDirect online access

Subtotal Journal Options \$ _____

Contribution

JR Robinson Contribution \$ _____

Scholarship Fund (optional)*

Your contribution will help support a graduate student studying the science of delivery of bioactives (Donations of \$100 or more receive print acknowledgement.)

36th Annual Meeting Graduate Student Travel Grant Contribution (optional)* \$ _____

Contributions of \$25 or more receive print acknowledgement.

* Your contribution may be tax deductible.
 CRS is a 501(c)(3) organization. Consult your tax advisor on how the current law applies to you.

Contribution \$ _____

Grand Total \$ _____

Payment Method

Total payment must accompany completed application.

Check enclosed made payable to Controlled Release Society
(Must be in U.S. dollars drawn on a U.S. bank)

Charge Grand Total above to my: Visa MC Am. Express

Credit Card Number _____

Expiration Date /
Month Year

Card Holder's Name _____

Agreement: I accept to receive information from CRS via e-mail, and acknowledge that my contact information will appear on the CRS website in the online membership directory, unless I have stated otherwise.

Applicant Signature Month/Year

Return form to: Controlled Release Society, 3340 Pilot Knob Road, St. Paul, MN 55121 U.S.A.

Telephone: +1.651.454.7250 • Facsimile: +1.651.454.0766 • E-mail: crs@scisoc.org • Website: www.controlledreleasesociety.org



Renew for 2009!

As a Member You Receive

Discounts

- Annual Meeting & Exposition member rates
- Annual Meeting & Exposition *Transactions* on CD
- Educational Workshop member rates
- Satellite Meeting member rates
- Complimentary subscription to the *CRS Newsletter*
- Significantly reduced subscription rates to the
 - *Journal of Controlled Release*
 - *European Journal of Pharmaceutics and Biopharmaceutics*
 - *Biomaterials*

Industry Connections

- Online membership directory
- Online job placement service
- Volunteering and leadership opportunities

Opportunities to Be Involved

- Become a mentor
- Volunteer on a committee
- Organize an Educational Workshop or Satellite Meeting
- Present an abstract
- Join a Local Chapter
- Submit a book proposal
- Review abstracts
- Chair a Podium Session

Contact CRS Headquarters Today
+1.651.454.7250



Already a member?
Encourage your
colleagues to join.

www.controlledreleasesociety.org

CRS Satellite Meeting Oral Multi-particulate Drug Delivery Systems: "Challenges and Opportunities"

Hilton Vienna Danube
March 24-25, 2009
Vienna, Austria

Generously Co-sponsored by



and Media Sponsor



Chairs: Ali Rajabi-Siahboomi, Colorcon, Inc., U.S.A.; and
Brigitte Skalsky, Evonik Industries, Germany

The oral cavity is the most preferred and convenient route of drug delivery; and therefore, solid oral dosage forms are most recommended by healthcare professionals and ideal for patient compliance. Amongst solid oral dosage forms, multi-particulate drug delivery systems have gained major pharmaceutical market share, due to their superior clinical performance, provision of various formulation options, and advances made in the multi-particulate technologies.

CRS has organized a two-day satellite meeting in Vienna, as a forum for technical exchanges around the challenges and opportunities that multi-particulate systems may have. We highly recommend you attend this event where internationally renowned multi-particulate experts will present and discuss their experiences and latest work on the subject. The topics will guide you in selecting the most appropriate technology attributes for your API, reducing formulation and process development time, and discussing how you should get your product to the market with sound science based data and robust formulation and production. Please make a note in your calendar and secure an early registration, as space is limited.

For more information on the event content, venue, and registration, please visit www.controlledreleasesociety.org/main/meetings/SatelliteMeetings/2009_03SatelliteMeeting.cfm. We look forward to seeing you in Vienna March 24-25, 2009.



Quality by Design¹

Raafat Fahmy² and Dennis Bensley

Quality by design (QbD) is the FDA's latest initiative to encourage the industry to improve drug quality and to potentially reduce regulatory operation costs. The QbD process incorporates quality into the product by carefully evaluating all critical quality attributes from the early stages of development and throughout the product's lifecycle. QbD is part of a broader FDA initiative: Pharmaceutical Quality for the 21st Century: A Risk Based Approach (www.fda.gov/oc/cgmp/#guidance).

QbD is an approach to manufacture a product by applying mechanistic understanding, including appropriate controls based on risk management in a modern quality system (International Conference on Harmonization ICH Q8, Q9, and Q10). QbD emphasizes a product lifecycle approach that links development, process qualification, and continuous maintenance of control for commercial production (ref. draft GFI Process Validation: General Principles and Practices).

Ultimately QbD allows one to build quality into a product, with a thorough understanding of potential manufacturing variables, the management of potential risks to product quality and performance, and the establishment of processes to mitigate the identified risks. The degree of regulatory flexibility depends on the manufacturer's demonstrated level of product and process understanding and controls used in the implementation of a modern quality system.

General steps to manufacture the ideal QbD drug product include

1. Know your drug product.

Establish a general target drug profile:

This includes identifying the therapeutic index, proposed dosage strength(s), dosage form(s), route of administration, pharmacokinetic characteristics of the drug product, and site of drug absorption. It is through this understanding that a sponsor can identify and control the critical quality attributes (CQAs) that impact *in vivo* product performance.

2. Risk assessment: Linking material attributes and process parameters to CQA.

This component involves the characterization of the physicochemical and functional attributes of excipients and

determines the compatibility of these excipients with the drug substance or active ingredient. The variability of these three interactions (physicochemical properties, manufacturing process, and product performance) should be managed to assure the quality of the finished drug product. It is important to identify all special causes of variability and manage them through prior knowledge, experimentation, and risk assessment of the material attributes and process parameters that can affect product CQAs. Risk assessment should be performed early in the pharmaceutical development process, subsequently communicated, and repeated as more information becomes available.

3. Establish in-process controls.

Strategies for in-process controls should be based on process understanding and should be able to reduce variability of the product and prevent contamination, including control of both critical material attributes and critical process parameters that affect the CQA (e.g., disintegration, on-line/at-line analyzer for ending granulation time, blend uniformity, ending drying time, particle size, and real-time monitoring of microbiological contaminants). Monitoring of the critical process parameter, therefore, is shifted upstream (i.e., during the manufacturing process itself), using an on-line monitoring system (e.g., NIR with chemometric modeling) to predict the critical quality attributes. It is also important to establish a meaningful sampling technique and frequency during the process and suitable statistical models for multivariate analysis (i.e., dataset with multiple independent and interacting factors). The assessment of the material attributes and the ability to control the critical process parameters may provide real-time release.

4. Establishing design space.

Design space is a multidimensional combination and interaction of input variables (e.g., material attributes and process parameters) that have been demonstrated to provide assurance of quality. Information gathered during pharmaceutical development studies and manufacturing experience may define the design space. The applicant proposes the design space to the regulatory agency as part of the application and approval process, as long as the product is manufactured within limits established by QbD, product quality, and performance. It is within this framework that the *ICHQ8 Guidance* document indicates that manufacturing within the design space is not considered a change; however, post-approval changes outside the approved design space usually initiates a regulatory change process and prior approval by the regulatory agency before implementation.

¹The views expressed in this article are those of the authors and do not reflect the official policy of the FDA. No official support or endorsement by the FDA is intended or should be inferred.

²Corresponding author. Center of Veterinary Medicine, Office of New Animal Drug Application; Tel: +1.240.276.8251; E-mail: Raafat.fahmy@fda.hhs.gov.

5. *Employ risk management.*

To mitigate the risk of sub-optimal product quality a control strategy is needed. This strategy involves defining the sources of variability in material attributes and the process parameters that affect product quality attributes throughout its lifecycle. Once the sources of variability (the stresses that affect quality) are known, these stresses should be monitored, controlled, and managed (e.g., establish reliability over the shelf life of the product by selecting the appropriate packaging system).

6. *Invest in a modern quality system.*

The FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, September 2006, describes what needs to be implemented in a modern quality system and the risk management approaches needed to comply with current good manufacturing practice regulations. To employ a lifecycle approach to the control of commercial manufacturing of a QbD product, a modern quality system must be employed. Only by implementing an appropriate modern quality system, coupled with a demonstration of product and process understanding and effective risk management practices, can the FDA consider a reduction in regulatory oversight. A modern quality system can be adjusted to address the scope and complexity of an operation, including limited resources.

Although there is an initial cost outlay associated with the implementation of QbD, this paradigm will not only likely increase the quality and safety of commercial products but, in the long term, should be cost-effective from a production/control standpoint. Through the mechanistic understanding of critical manufacturing information, employment of the tools of risk analysis, and subsequent utilization of combined control strategies, manufacturers can reduce burdens associated with regulatory oversight and optimize the cost-effectiveness and efficiency of their manufacturing processes. ■

CRS Education Meets Your Needs

Educational Workshops

These workshops will precede the 36th Annual Meeting & Exposition of the Controlled Release Society at the Bella Center in Copenhagen, Denmark.

Saturday, July 18

Educational Workshop 1:

RNA Interference Biology and Therapeutics

Chaired by Ken Howard, Interdisciplinary Nanoscience Center (iNANO at the University of Aarhus, Denmark; and Jørgen Kjems, Interdisciplinary Nanoscience Center (iNANO at the University of Aarhus, Denmark)

Saturday, July 18 and Sunday, July 19

Educational Workshop 2:

Imaging in Drug Development

Chaired by Ole Hjelstuen, University of Tromsø/GE Healthcare, Norway; and Susanna Abrahmsén Alami, AstraZeneca, Sweden

Educational Workshop 3:

In Vivo Dissolution—Is It a Reality? Can It Be Correlated to In Vitro or In Silico DISSOLUTION?

Chaired by Daniel Bar-Shalom, IPC International Operations A/S, Denmark; and Anette Müllertz, Bioneer:FARMA, Denmark

Educational Workshop 4:

Micro and Nano Encapsulation

Chaired by Christopher Barbe, Ceramisphere Pty Ltd, Australia; and Teresa Virgallito, Microtek Laboratories, U.S.A.

Separate registration is required for CRS educational workshops. Register by May 4, 2009, for the best registration rates for the educational workshops and the annual meeting and exposition.



www.controlledreleasesociety.org

Young Scientists Mentorship Program Calling All Protégés!

*Michael Rathbone, Ozgen Ozer, Sudip Das, and Teresa Virgallito
Young Scientist Mentor/Protégé Subcommittee*

CRS Young Scientists Mentorship Program

The CRS has established a Young Scientists Mentorship Program that is designed to advance the personal and professional development of its young scientists through the establishment of meaningful relationships between them and experienced members of the CRS. The CRS Young Scientists Mentorship Program is open to all scientists 40 years or younger and those scientists who have joined the area of controlled release within the previous five years.

The CRS Young Scientists Mentorship Program is an outcome of a successful 1-year pilot program that involved four mentor-protégé pairs that was conducted during 2007–2008. After it was observed that the career development of the four young scientists significantly benefited from their mentorship relationships, it was decided to expand the program to involve at least 20 pairs and offer it as a member benefit to any and all newly joined members of the CRS. It is the aim of the program to increase the number of pairings on an annual basis to accommodate the perceived demand that this program will command. The CRS Young Scientists Mentorship Program is run by the CRS Mentor/Protégé Subcommittee (Mike Rathbone, Ozgen Ozer, Sudip Das, and Teresa Virgallito).

What Is Mentorship?

Mentorship is an intentional relationship between a more experienced person (referred to as a mentor) and a less experienced person (referred to as a protégé) with the goal of developing the protégé's personal and professional skills in a nurturing and supportive manner. Mentorship generally involves a single mentor and a single protégé in a one-on-one relationship.

History of Mentorship

Mentorship is believed to have evolved from the character of Mentor in Homer's *Odyssey*. Although Mentor himself is a somewhat ineffective old man, the goddess Athena takes on Mentor's appearance in order to guide young Telemachus through his time of difficulty.

Famous mentor-protégé pairs in history include Socrates and Plato, Plato and Aristotle, and Aristotle and Alexander the

Great. Well-recognized CRS relationships involving mentors and protégés (who themselves became well established in the field of controlled release drug delivery) include Joe Robinson and Kinam Park, Sandy Florence and Ijeoma Uchegbu, and Bob Davis and Diane Burgess.



Networking – Providing opportunities to be introduced to, and interact with, the world's best controlled release scientists and technologists.

Using its Young Scientists Mentorship Program, the CRS offers young scientists the opportunity to become involved in the CRS and stand on the shoulders of more experienced CRS members.

What Forms Do Mentorship Relationships Take?

There is a wide variety of forms that a mentorship relationship can take. The form depends on the context and personalities involved; however, the

overall intention of most mentorship programs is that they should be

- Intentional
- Supportive
- Associated with some form of structured process
- A nurturing process to the protégé
- An insightful and reflective process on behalf of the mentor

What Is the Role of the Mentor?

The role of the mentor is to facilitate the personal and professional development of the protégé. The mentor achieves this by being a guide, rather than a provider of knowledge. A

mentor is someone who encourages and counsels when it is required. In essence, the mentor provides a supportive function as a helping hand. The mentor provides such support to the protégé by implementing strategic actions as opposed to a formal training activity.

What Is the Role of the Protégé?

The role of the protégé is to hold the helping hand of the mentor. A protégé has to be interactive with their mentor,

to be willing to discuss and to learn from their mentor, and to maintain regular contact with them. The protégé works as a partner and has to stimulate the mentor with their expectations, passion, and keen interest.



Involvement – Offering the chance to become involved in CRS activities, providing visibility and leading to further opportunities.

Value of Being a Protégé

The value of being a protégé in the CRS Young Scientists Mentorship Program is shown in Figure 1. Networking is an important way of developing and building a group of contacts that can help provide career information and opportunities. Being a part of the CRS Young Scientists Mentorship Program allows the protégé to build their network and connect with an extensive group of worldwide members of the CRS who can provide them with guidance, knowledge, and the opportunity to help them succeed.

How Does the CRS Young Scientists Mentorship Program Work?

The protégé has an opportunity to be partnered with a more experienced member of the CRS at the CRS Annual Meeting & Exposition (generally in June or July each year). Registration for the CRS Young Scientists Mentorship Program takes place at a special Young Scientists Morning Coffee Meeting held during the CRS Annual Meeting & Exposition.

At the Young Scientists Morning Coffee Meeting, protégés are given an overview of the program and an application form to complete. The information in the form is used to help determine the most suitable mentor to ensure the best partnership. A short time after the Young Scientists Morning Coffee Meeting, the protégé attends a Meet and Greet Session and is notified of the identity of their mentor. At this time, the young scientist is provided with the opportunity to meet their mentor face-to-face.

After the partnership has been established, it is the responsibility of the protégé to contact their mentor regularly to benefit from the relationship.

What Are the Expectations?

On the protégé's part, they can expect to be provided with a great opportunity to develop their professional network and to learn from their mentor's years of experiences—however, the protégé should not expect to land a job or an interview through this program. The protégé can expect to be paired with a mentor



Career Development – Providing experienced help with your first steps toward a rewarding career in controlled release science and technology.

who will be committed to meeting with them at least once a month for 12 months—however, do not expect the mentor to run after the protégé. It is the protégé's responsibility to drive the process to achieve the desired results by scheduling meetings, developing an agenda, and taking the time to research what they would like to discuss and learn from their mentor.

The protégé can expect the CRS to match them up and introduce them to an outstanding mentor with years of controlled release science and technology experience, but do not expect to see structured guidelines for the relationship. To achieve the maximum benefit from the partnership, the CRS Young Scientists Mentorship Subcommittee has designed the mentorship program simply to facilitate the partnership.

On CRS's part, we expect from each protégé a 12-month commitment and two update reports—one at 6 months and one at the end of the term.

Future Activities of the CRS Young Scientists Mentor/Protégé Subcommittee

The Young Scientists Mentorship Program presents an excellent chance for young scientists to get involved in the CRS at an early stage in their careers. The opportunity to interact and work with well-known scientists from all over the world in a program that is designed to be flexible and adapt itself to the protégé offers a great opportunity for young scientists. The program is continually being reviewed, developed, and expanded to ensure that it meets future demands. This is the responsibility of the CRS Young Scientists Mentor/Protégé Subcommittee. Some of their planned future activities include:

- Development of induction workshops to provide protégés with guidance and information that support their year of participation
- Provision of mechanisms for online support so protégés are aware of their responsibilities and requirements
- Design of web-based materials to provide further mentorship advice
- Development of exciting and innovative CRS Annual Meeting & Exposition activities specifically for protégés on topics related to mentorship
- Provision of regular *CRS Newsletter* articles on topics of interest on mentorship
- Design of a coaching program to be delivered at a future CRS Annual Meeting & Exposition

Bottom line

GET INVOLVED! Expressions of interest in participating in the Young Scientists Mentorship Program can be sent at anytime to Ronda Thompson (rthompson@scisoc.org). Your name will be kept on record, and you will personally be informed of the day, date, and time of the next Young Scientists Morning Coffee Meeting. ■

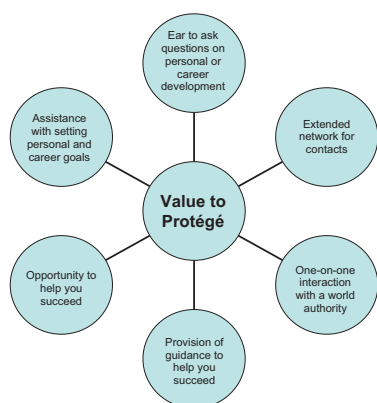


Figure 1. The value of being a protégé in the CRS Young Scientists Mentorship Program.

“If I have seen far, it is because I stand on the shoulders of giants.”

—Sir Isaac Newton

Report on the 2nd AUS-CRS Annual Meeting

*Pavla Simerská,¹ M.Sc., Ph.D.
Scientific Secretary, AUS-CRS*

On behalf of the Australian Chapter of the Controlled Release Society (AUS-CRS), I would like to report to you on the success of our 2nd AUS-CRS Annual Meeting, which was held in conjunction with the Australasian Pharmaceutical Science Association (APSA) Conference on Sunday, December 7, 2008, at the Australian National University in Canberra. Created in July 2007, AUS-CRS is a young chapter in the CRS organization, yet the quality of the program was outstanding.



Professor Istvan Toth (AUS-CRS president) opens the 2nd AUS-CRS Annual Meeting.

The AUS-CRS 2nd Annual Meeting was opened by Prof. Istvan Toth (AUS-CRS president), followed by a plenary lecture given by Prof. Thomas Rades (NZ-CRS president). In addition to nine invited highly recognized national speakers (Mark von Itzstein, Robert Capon, Benjamin Thierry, Calum Drummond, Paul Young, Michael Rathbone, Angus Johnston, Chris Porter, and Michael Roberts), we were also very fortunate to have an imminent international guest, Prof. Paolo Colombo (University of Parma, Italy).

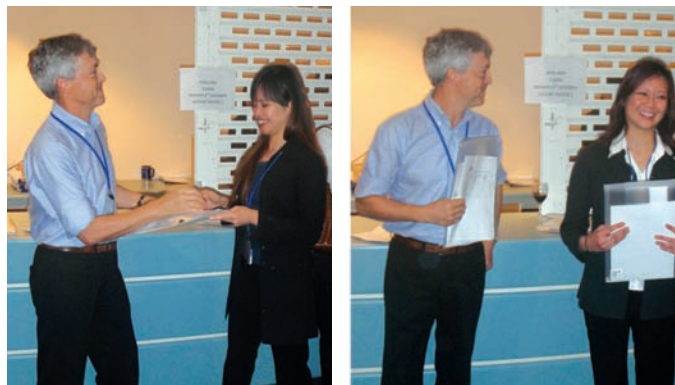
During the annual General Meeting, past and future AUS-CRS activities were discussed, as well as how to improve and expand the local chapter, finances, and the strategy for the 2009 meeting (separate or in conjunction with APSA). It was also decided that the AUS-CRS committee will remain the same for another year, and then elections will be organized following the CRS model.

This meeting provided opportunities for students and researchers from both academia and industry to discuss recent developments in the controlled release field. We thank our generous sponsors: Institute of Pharmaceutical Sciences, Monash University; School of Pharmacy, The University of Queensland; Faculty of Pharmacy, The University of Sydney; Queensland University of Technology; and School of Pharmacy, Griffith University. Their support enabled us to organize this conference and to provide four student prizes for the best posters in the controlled release field:

1st Prize: The University of Queensland, School of Pharmacy Prize \$1,000 – Contribution toward attending the 2009 CRS Annual Meeting & Exposition in Copenhagen – awarded to

¹School of Molecular and Microbial Sciences, The University of Queensland, Brisbane, QLD 4072, Australia; Tel: +61 7 3346 9893; Fax: +61 7 3365 4273; E-mail: p.simerska@uq.edu.au.

Photos by Pavla Simerska.



Allan Coombes (AUS-CRS secretary) awards the 1st poster prizes (top) to Kathy Lee and Angel Tan (from left); and the 2nd and 3rd poster prizes (bottom) to Hemant Kumar and Thilini Thrimawithana (from left).

Kathy Lee, Monash Institute of Pharmaceutical Sciences (“Gastric Processing Is a Critical Determinant of the Ability of Lipid-based Formulations to Enhance the Oral Bioavailability of a Model Poorly Water-Soluble Drug”).

1st Prize: The University of Sydney, Faculty of Pharmacy Prize \$1,000 – Contribution toward attending the 2009 CRS Annual Meeting & Exposition in Copenhagen – awarded to Angel Tan, Ian Wark Research Institute (“Silica-Lipid Hybrid Microcapsules for Oral Delivery of Poorly Soluble Drugs”).

2nd prize: Queensland University of Technology, Pharmacy Prize \$300 – Awarded to Hemant Kumar, The University of Auckland (“Oral Formulation of Lactoferrin, a Bioactive Peptide from Lactoferrin, a Whey Protein and Its *In-Vitro* Release Studies”).

3rd Prize: Griffith University, School of Pharmacy Prize \$200 – Awarded to Thilini Thrimawithana, School of Pharmacy, University of Auckland (“Texture Profile Analysis of Kappa and Iota Carrageenan Gels”). ■

CRS–Illinois Student Chapter Holds Social Event



From left to right: Subhair Sunogrot, Misuk Bae, Ramana Vishnubhotla, Rezene Asghodom, and Amrita Banerjee.

The Controlled Release Society–Illinois Student Chapter, formerly the Chicago Student Chapter, hosted a social event on November 21, 2008, in the College of Pharmacy at the University of Illinois at Chicago (UIC). The CRS–Illinois Student Chapter decided to change its name during the 2008 chapter meeting, with the goal of extending its activities to the entire region of Illinois, in addition to the Chicago area. The social event organized by the Illinois Student Chapter was a “game night,” with sponsorship from the Chicago Organization Fund (COF). The COF committees reviewed the application and decided upon a fund based on a presentation that competed with other student organizations at UIC. Approximately 15 students attended the event and came from a variety of departments, including Bioengineering, Biopharmaceutical Sciences, Medicinal Chemistry, Pharmacognosy, and Pharmacy.

The CRS–Illinois Student Chapter currently has 20 members, including 4 board members (President Misuk Bae, Vice President Amrita Banerjee, Secretary Kristin Thomas, and Treasurer Ramana Vishnubhotla) and a faculty advisor (Dr. Richard A. Gemeinhart).

The chapter plans two seminars and a one-day symposium in spring 2009. The recent news of the CRS–Illinois Student Chapter is updated at www2.uic.edu/stud_orgs/prof/crs/index.htm. ■

CRS New Zealand and Australian Chapters Hold Joint Workshop on Peptide and Protein Bioactives—Stability and Delivery

Hemant Kumar¹ and Rohit Jain²

Over 70 delegates in Brisbane, Australia (October 6–7, 2008), and over 40 in Dunedin, New Zealand (October 9–10, 2008), from academia and industry, participated in the science-intensive, and enjoyable two-day workshop on Peptide and Protein Bioactives – Stability and Delivery. The workshop offered an excellent opportunity for students and industry representatives working in the field of protein and peptides formulation and delivery to enhance cooperation between academia and industry. The workshop began with a welcome from Dr. Natalie Medlicott (University of Otago) and the presidents of both the New Zealand and Australian Local Chapters of CRS, Prof. Thomas Rades (New Zealand) and Prof. Istvan Toth (Australia). The introductory presentation was given by Dr. Louise Rosenmayr–Templeton (director of Tower Pharma Consulting) on industrial perspectives and recent approaches for protein formulation. Dr. Rosenmayr–Templeton informed the audience about the market potential of protein and peptide therapeutics and gave an overview on the bench and scale-up formulation challenges for protein and peptide products. Current research was addressed by Dr. Pavla Simerska (The University of Queensland) on the different delivery systems and current issues in peptide formulation and delivery. Different methods for altering the chemical structure of peptides to improve bioavailability was given considerable, well-received attention.

Prof. Thomas Rades (University of Otago) and Dr. Medlicott presented insights into the stability of protein and peptides in solid state and in solutions, respectively. The talks were very informative for both researchers and those in industry, covering



Left to right: workshop speakers Dr. Natalie Medlicott, Dr. Arlene McDowell, Prof. Thomas Rades, Dr. Louise Rosenmayr–Templeton, Dr. Pavla Simerska, and Prof. Istvan Toth. Photo by Julie Bergeon.

¹School of Pharmacy, University of Auckland, New Zealand.

²School of Pharmacy, University of Otago, New Zealand.



Anshul Awasthi demonstrates SDS-PAGE electrophoresis to Dunedin workshop attendees Rinku Singh and Lipika Chatterjee. Photo by Arlene McDowell.

the major and minor pathways of protein and peptide degradation and different techniques and instruments suitable for characterising protein and peptide degradation. Dr. Medlicott presented a second talk emphasising proof of concept and discussed in detail the assessment of proteins in formulation, giving examples of major stability issues.

The afternoon session on the first day focused on two aspects: first, assessment of bioactivity of peptides and proteins; and second, instrument demonstrations. Dr. Arlene McDowell (University of Otago) presented aspects of the pharmacokinetics of protein and peptide formulations and provided the audience with detailed information about bioassays, toxicity studies, and *in vitro* and *in vivo* models. Later in the afternoon a panel discussion was opened, and the audience shared their knowledge, expertise, and experiences with protein and peptide formulations. Immediately after the afternoon tea, the audience toured laboratories to look at instruments that are primarily employed to characterise protein formulations in terms of protein and peptide stability, e.g., LCMS, FTIR, HPLC, and SDS-PAGE.



Dr. Natalie Medlicott thanks guest speaker Dr. Louise Rosenmayr-Templeton for her contribution to the workshop. Photo by Arlene McDowell.

The session on the second day was opened by Dr. Rosenmayr-Templeton, who delivered a very interesting talk about what to consider when selecting the delivery route, formulation approach, and developing formulation. She gave an account of different devices used in or in development for the delivery of proteins and peptides and spoke about the different routes of administration, different barriers for protein therapeutics and formulation strategies, and different delivery systems. Prof. István Toth (The University of Queensland) presented some very novel approaches to improve vaccine delivery, bringing to our attention the early days of vaccine development and recent approaches (such as lipopeptides) and their role as adjuvants. The morning's



Participants at the Brisbane workshop discuss the group case studies. Photo by Pavla Simerska.

last presentation by Dr. Rosenmayr-Templeton focused on practical examples of improving delivery of protein therapeutics. The day wrapped up in the afternoon with the audience assigned to small groups to discuss and address a number of case studies associated with the characterisation and formulation of proteins and peptides. These case studies were approached with enthusiasm and led to some very intense discussions.

The workshop was closed by Drs. Medlicott and Simerska, who thanked everybody for their help and participation and invited everyone to attend and participate in future chapter meetings.

For a stimulating and interesting workshop, we thank the speakers, organisers of the workshop, those who helped with the instrument demonstration sessions, as well as the co-sponsors: School of Pharmacy, University of Otago; Formulation and Delivery of Bioactives Research Theme, University of Otago; School of Pharmacy, The University of Queensland; and Faculty of Biological & Chemical Sciences, The University of Queensland. ■

C&DP Committee

Dr. Claudio Ortiz¹

Program Co-chair 36th CRS Annual Meeting & Exposition

Have you ever seen the acronym above and wondered “what does it mean?” Well the literal meaning is Consumer and Diversified Products. The simplest way to describe it is: applications of controlled release to anything that does not have a pharmaceutical or veterinary application. This does not mean that you can’t use the knowledge and applications used in other products and apply it to the “pharma” and “vet” fields. The C&DP field is universal, meaning it encompasses applications for any field of study, from consumer products to agriculture and paints to food. In the end, because it is in an all-inclusive field there are presentations with applications in the “pharma” and “vet” fields as well.

We are very excited about the sessions we have organized for the 36th CRS Annual Meeting & Exposition to be held in Copenhagen, Denmark, in July 2009. If you are planning to come to the meeting, you don’t want to miss attending at least one of the sessions that interest you. If you are not planning to come, then maybe you should change your mind and start preparing for the trip.

Below is a sample of the variety and caliber of speakers from all areas of controlled release who are participating in the program.

Technical Program—Sessions and Invited Speakers

- 1) **Advances in Process Technology**
Bojana Boh, University of Ljubljana, Slovenia
Research and innovation trends in microencapsulation
- 2) **Controlled Release for Textiles**
Raymond Mathis, Cognis GmbH, Germany
Delivery of micro-encapsulated cosmetic ingredients from textiles to the skin
- 3) **Evaluation of Controlled Release Products**
Andreas Degenhardt, Symrise, Germany
Benchmarking methods of particles
- 4) **Micro and Nano Particles**
Jens Uhlemann, Bayer, Germany
Options and applications for nanoscale delivery systems
- 5) **Uniquely Original Delivery Systems**
Gleb Sukhorukov, Queen Mary University, U.K.
Multifunctional cargo systems: Polyelectrolyte based multilayer microcapsules
- 6) **Future Directions for Controlled Release**
Igor Bodnar, NIZO, The Netherlands
Protect and deliver probiotics; Encapsulation of living micro organisms

If you are looking for basic knowledge and understanding on how controlled release works and the basic science behind it, together with applications, then you can’t miss the educational workshop organized by the C&DP Committee “Micro and Nano Encapsulation” as part of the Copenhagen meeting. The two-day educational workshop will be held on Saturday, July 18, and Sunday, July 19, 2009.

The C&DP Committee is a hard-working group of people who are also fun to be around. A meeting like this can’t be complete without “networking,” and this group of people is the best at doing it. There is always a special group lunch—one of the best opportunities to informally meet new people. If you are interested in coming, just ask any of the session moderators for information on the “group lunch” that will take place on Tuesday, July 21. There will be plenty of other opportunities to network with this group, and if you like what you see and want to get involved, then come to our committee meeting for an hour and get to know in more detail how the committee works. ■



Pharmaceutics Faculty Positions for the Texas A&M Health Science Center (HSC)

The Texas A&M Health Science Center Irma Lerma Rangel College of Pharmacy in association with the Center for Microencapsulation and Drug Delivery of the Texas A&M Health Science Center College of Medicine is seeking dynamic individuals for two tenure-track senior research faculty positions in Bryan/College Station, Texas.

Applications are invited from individuals with experience, demonstrated leadership, and vision to develop research in the areas of pharmaceutics, drug formulations, industrial pharmacy, drug delivery, biopharmaceutics or related areas of product development. The Center for Microencapsulation and Drug Delivery is focused on integrating the discoveries, translational research, and pharmaceutical development of basic scientists, pharmaceutical scientists, and clinicians within the Health Science Center and other components of the Texas A&M System. Therefore, it is essential that the candidates have a broad understanding of drug and vaccine product development and an ability to steer the A&M discoveries into product development with collaborative research and scientific leadership. Candidates selected will have ample opportunities to develop and strengthen a world-class Center for Microencapsulation and Drug Delivery and Pharmaceutical Product Development with additional faculty and research resources/partnerships.

The successful candidates are expected to be well-known leaders with national and international recognition within the general areas of pharmaceutics and product development; have an earned doctorate degree in the related disciplines of pharmaceutics, industrial pharmacy, physical pharmacy, or biopharmaceutics; have a record of very successful grant activities from federal, state, and industrial sources; have an extensive publications record; show evidence of successful mentoring of junior faculty, post docs, and graduate students; and display a demonstrated ability to work with other disciplines, pharmacy industry, and drug regulating agencies.

Besides teaching and mentoring responsibilities for Pharm.D. and graduate students, key deliverables of this position include an ability to develop a strong, well-funded independent research program; develop a new product development center with federal, state, industrial, and institutional grants; recruit and train junior faculty and graduate students; facilitate the discovery and development of therapeutic drugs by faculty within the Texas A&M System; serve as a national and international leader to promote the education and research interests of the College of Pharmacy and College of Medicine within the Texas A&M Health Science Center; and be a champion for pharmaceutical product development in the 21st century.

Review of applications will begin January 15, 2009, and continue until suitable candidates are identified. Applicants should send a letter of interest, curriculum vita, description of research interests, and names and contact information for five references to: **Pharmacy Senior Faculty Search; Texas A&M Health Science Center; 101 Gateway Blvd., Ste. A, College Station, TX 77840.** Electronic applications are preferred. Email: PFPP@medicine.tamhsc.edu URL: <http://cmdd.tamu.edu>

The Texas A&M Health Science Center is an Affirmative Action/Equal Access/Equal Opportunity Employer committed to diversity and excellence.

¹Colgate Palmolive, Piscataway, NJ, U.S.A.

Top Five Downloaded Research and Review Articles in the *Journal of Controlled Release*

Morgan Fischer and Steven Schwendeman

As a new year begins, the editors of the *Journal of Controlled Release* (JCR) reflect back on which articles were popular in 2008. Based on data gathered from January to August 2008, the following list reflects the top downloaded JCR articles during this time frame. Manuscripts based on water-soluble and nanoscale polymeric delivery systems, particularly for delivery of anticancer and nucleic acid-based drugs, occupy the top spots.

Top 5 Research Articles

1) Efficient Gene Silencing in Metastatic Tumor by siRNA Formulated in Surface-Modified Nanoparticles

Shyh-Dar Li, Sumio Chono, and Leaf Huang

A nanoparticle (NP) formulation, prepared in a self-assembling process, for systemically delivering siRNA into metastatic tumors was modified by PEG-lipid containing a targeting ligand, anisamide, and thus was decorated for targeting sigma receptor expressing B16F10 tumor. While confocal microscopy showed that the naked NP provided no tissue selectivity and non-targeted NP was ineffective for tumor uptake, the targeted NP effectively penetrated the lung metastasis, but not the liver. It resulted in 70–80% gene silencing in the metastasis model after a single i.v. injection (150 µg siRNA/kg).

2) Antitumor Efficacy of Cisplatin-Loaded Glycol Chitosan Nanoparticles in Tumor-Bearing Mice

Jong-Ho Kim, Yoo-Shin Kim, Kyeongsoon Park, Seulki Lee, Hae Yun Nam, Kyung Hyun Min, Hyung Gon Jo, Jae Hyung Park, Kuiwon Choi, Seo Young Jeong, Rang-Woon Park, In-San Kim, Kwangmeyung Kim, and Ick Chan Kwon

To make a tumor-targeting nano-sized drug delivery system, biocompatible and biodegradable glycol chitosan ($M_w = 250$ kDa) was modified with hydrophobic cholanic acid. The resulting hydrophobically modified glycol chitosans (HGCs) that formed nano-sized self-aggregates in an aqueous medium were investigated as an anticancer drug carrier in cancer treatment.

3) Hydrophobically Modified Glycol Chitosan Nanoparticles-Encapsulated Camptothecin Enhance the Drug Stability and Tumor Targeting in Cancer Therapy

Kyung Hyun Min, Kyeongsoon Park, Yoo-Shin Kim, Sang Mun Bae, Seulki Lee, Hyung Gon Jo, Rang-Woon Park, In-San Kim, Seo Young Jeong, Kwangmeyung Kim, and Ick Chan Kwon

To prepare a water-insoluble camptothecin (CPT) delivery carrier, hydrophobically modified glycol chitosan (HGC) nanoparticles were constructed by chemical conjugation of hydrophobic 5β-cholanic acid moieties to the hydrophilic glycol chitosan backbone. Insoluble anticancer drug, CPT,

was easily encapsulated into HGC nanoparticles by a dialysis method, and the drug loading efficiency was above 80%.

4) The Use of Fluorescence Microscopy to Define Polymer Localisation to the Late Endocytic Compartments in Cells that Are Targets for Drug Delivery

Simon C. W. Richardson, Kerri-Lee Wallom, Elaine L. Ferguson, Samuel P. E. Deacon, Matthew W. Davies, Alison J. Powell, Robert C. Piper, and Ruth Duncan

The aim of this study was to define a fluorescence microscopy technique able to confirm the localisation of water-soluble polymeric carriers to late endocytic intracellular compartments. Three polymeric carriers of different molecular weight and character were studied: dextrin ($M_w \sim 50,000$ g/mol), a *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer ($M_w \sim 35,000$ g/mol), and polyethylene glycol (PEG) (M_w 5000 g/mol). The technique described here is a particularly powerful tool, as it circumvents fixation artifacts ensuring the retention of water-soluble polymers within the vesicles they occupy.

5) Tumor Targetability and Antitumor Effect of Docetaxel-Loaded Hydrophobically Modified Glycol Chitosan Nanoparticles

Ho-Young Hwang, In-San Kim, Ick Chan Kwon, and Yong-Hee Kim

Hydrophobically modified glycol chitosan (HGC) nanoparticles, a new nano-sized drug carrier, were prepared by introducing a hydrophobic molecule, cholanic acid, to water-soluble glycol chitosan. The HGC nanoparticles were easily loaded with the anticancer drug docetaxel (DTX) using a dialysis method, and the resulting docetaxel-loaded HGC (DTX-HGC) nanoparticles formed spontaneously self-assembled aggregates with a mean diameter of 350 nm in aqueous condition. The DTX-HGC nanoparticles exhibited a distinctive deformability in aqueous conditions, in that they could easily pass through a filter membrane with 200-nm pores despite their mean diameter of 350 nm.

Top Five Reviews

1) *In Situ* Gelling Stimuli-Sensitive Block Copolymer Hydrogels for Drug Delivery

Chaoliang He, Sung Wan Kim, and Doo Sung Lee

This review focuses on recent developments in the preparation and application for drug delivery of the block copolymer hydrogels that respond to temperature, pH, or both stimuli, including poly(*N*-substituted acrylamide)-based block copolymers, poloxamers and their derivatives, poly(ethylene glycol)-polyester block copolymers,

polyelectrolyte-based block copolymers, and the polyelectrolyte-modified thermo-sensitive block copolymers.

2) Nano/Micro Technologies for Delivering Macromolecular Therapeutics Using Poly(d,l-lactide-co-glycolide) and Its Derivatives

Raghavendra C. Mundargi, V. Ramesh Babu, Vidhya Rangaswamy, Pradip Patel, and Tejraj M. Aminabhavi

In this review, important findings of the past decade on the encapsulation and release profiles of macromolecular therapeutics from PLGA and PLGA-based nano/microparticles are discussed critically in relation to nature and type of bioactive molecule, carrier polymer, and experimental variables that influence the delivery of macromolecular therapeutics.

3) Biodegradable Polymeric Nanoparticles as Drug Delivery Devices

Kumaresh S. Soppimath, Tejraj M. Aminabhavi, Anandrao R. Kulkarni, and Walter E. Rudzinski

This review presents the most outstanding contributions in the field of biodegradable polymeric nanoparticles used as drug delivery systems.

4) Biodegradable Polymers as Non-viral Carriers for Plasmid DNA Delivery

Jordy Luten, Cornelius F. van Nostrum, Stefaan C. De Smedt, and Wim E. Hennink

In this article the recent results obtained with two classes of degradable gene delivery systems, namely those based on water-soluble cationic polymers and on micro- and nanoparticles, are summarized and discussed.

5) A Review of Stimuli-Responsive Nanocarriers for Drug and Gene Delivery

Srinivas Ganta, Harikrishna Devalapally, Aliasgar Shahiwala, and Mansoor Amiji

In this review, the role of stimuli-responsive nanocarrier systems for drug and gene delivery is discussed. ■

Look to the Future with CRS!

Oral Multi-Particulate Drug Delivery Systems: Challenges and Opportunities

March 24-25, 2009
Hilton Vienna Danube
Vienna, Austria

36th Annual Meeting & Exposition of CRS

July 18-22, 2009
Bella Center
Copenhagen, Denmark

37th Annual Meeting & Exposition of CRS

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

38th Annual Meeting & Exposition of CRS

July 30-August 3, 2011
Gaylord National Resort and Convention Center
National Harbor, Maryland, U.S.A.



Pharmaceutical Sciences and Biotechnology

Diksha Kaushik,¹ Agis Kydonieus,² Vishwas Rai,¹ and Bozena Michniak-Kohn¹

We reviewed numerous U.S. patents issued in 2008 in the field of pharmaceutical sciences and biotechnology. We have attempted to list most of them according to their route of delivery, such as oral, parenteral, transdermal, ocular, inhalation, etc. We have also listed patents issued related to targeted drug delivery at the organ and gene level and some patents issued to drug delivery devices, processes, and systems. The current update also contains a list of certain patents that claim discovery of novel compounds with significant pharmacological activities.

NOVEL DELIVERY SYSTEM ADMINISTERED BY ORAL ROUTE

Oral Insulin Therapy (Emisphere Technologies, Inc.) US 7429564

The patent claims development of an oral insulin therapy. The delivery agent may be used directly by mixing one or more such agents with the active agent (e.g., unmodified insulin) prior to administration. The patent states that the delivery agent and active agent may be mixed in dry powder form or by means of wet granulation with the addition of other pharmaceutically acceptable excipients. The mixture may then be tableted or placed into gelatin capsules containing a unit dose of the active agent and the delivery agent, or the delivery agent/active agent mixture may be formulated as an oral solution or suspension. The patent claims that the novel formulation is therapeutically effective and results in a lower incidence of vascular diseases associated with the repeated administration of insulin in conventional therapy.

Orally Active Peptides that Prevent Cell Damage and Death (National Institutes of Health) US 7384908

This patent discloses the composition of a formulation containing an activity dependent neurotrophic factor (ADNF) polypeptide with active core site having at least one D-amino acid. The invention claims to be orally active and possess properties of reducing neuronal cell death, oxidative stress, and a condition associated with fetal alcohol syndrome.

Delivery of Multiple Doses of Medications (Celgene Corporation) US 7431944

The current patent describes the dosage forms involving oral administration of a methylphenidate drug. The invention involves release of an initial dose of a drug (d-threo-methylphenidate) followed by an interval wherein substantially no additional drug is released, followed by release of a second dose. The patent states that if desired, a second substantially release-free interval may be provided following the second release, followed by a third dose. Hence the patent claims provision of three or more doses in a single dosage unit.

Controlled Release Formulations Having Rapid Onset and Rapid Decline of Effective Plasma Drug Concentrations (Purdue Pharma) US 7438930

The patent claims the development of oral modified/controlled release drug formulations that provide a rapid initial onset of effect and a prolonged duration of effect. The patent claims that the new formulation depicts a lower peak concentration than that provided by the reference standard for immediate release formulations of the drug, and the duration of effect falls rapidly at the end of the dosing interval. The patent states that the controlled/modified release drug formulations consist of beads that include an immediate-release component and an enteric-coated controlled-release component to produce a delay in the absorption process. The drug product is an oral capsule containing beads, with each bead containing a series of layers with different release characteristics—an outer immediate release layer; a release delaying layer; a controlled release layer; and an immediate release core.

Nanoparticulate Topiramate Formulations (Elan Pharma International, Ltd.) US 7390505

The patent discloses nanoparticulate compositions comprising topiramate (anticonvulsant). The topiramate particles of the composition have an effective average particle size of less than about 2 μm . The patent claims that nanoparticulate topiramate can be administered by oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, or topical route.

Method for Controlling Body Weight in Estrogen-Insufficient Women (Abbott Laboratories) US 7435431

The patent describes methods of controlling body weight in estrogen-insufficient women (due to menopause, ovariectomy, ovarian disorders, and drug treatments) by administering compositions comprised of (A) dried fruit solids that inherently contain flavonoids, hydroxycinnamic acids, and a fiber component of which at least about 20% by weight is soluble fiber, and (B) a soluble, indigestible oligosaccharide in addition to any soluble fiber inherently in the dried fruit solids (dried plum, dried grape, dried date, or dried fig). The patent states that administration of dried fruit solids (e.g., dried plum solids) in combination with soluble indigestible oligosaccharides (e.g., fructooligosaccharides) is surprisingly effective in controlling body weight gain and bone mineral density in estrogen-insufficient women. The patent states that the nutritional compositions of components mentioned above, therefore, can be formulated with reduced concentrations of dried fruit solids, while still maintaining an ability to affect bone mineral density and controlling body gain provided that the dried fruit solids are used in combination with a soluble indigestible oligosaccharide component such as fructooligosaccharides.

¹Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, NJ, U.S.A.

²Samos Pharmaceuticals, LLC, Kendell Park, NJ, U.S.A.

Ondansetron Orally Disintegrating Tablets (Barr Lab Inc.) US 7390503

The invention provides a non-effervescent, solid orally disintegrating dosage form and process for forming an ondansetron solid disintegrating tablet adapted for oral administration to mammals. The dosage form is composed of a drug, at least one hydrophilic component (such as microcrystalline cellulose), a component having a -CHOH functional group (e.g., mannitol, xylitol), a disintegrating agent (such as crospovidone), and a water-insoluble component, optionally a lubricant and a sweetener. The lubricant may be a mixture of magnesium stearate, sodium stearyl fumarate, and colloidal silicon dioxide. The patent claims development of an ondansetron containing non-effervescent orally disintegrating dosage form effective in the treatment of emesis (nausea and vomiting) caused by cancer chemotherapy and radiation or in the case of mental disorders.

Pharmaceutical Formulation Comprising Lanthanum Compounds (Shire Biochem Inc.) US 7465465

This invention relates to a chewable lanthanum formulation that can be taken with no or limited amounts of liquid and is palatable to the patient, especially under conditions when it is administered in as dry a form as possible. The formulation comprises a pharmaceutically effective amount of a lanthanum compound and at least one chewable pharmaceutically acceptable excipient. It is for patients with end-stage renal disease or chronic kidney diseases that can have limited liquid intake. The patent also describes the following steps involved in preparation of the tablet formulation of lanthanum: (A) blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture; or (B) compressing the resulting combination into a slug material or roller-compacting the resulting combination into a strand material and milling the prepared material into a free-flowing mixture; and (C) compressing the resulting mixture into a tablet or filling up the resulting mixture in an appropriate container.

Pharmaceutical Gallium Compositions and Methods (Genta Incorporated) US 7456215

The invention provides novel pharmaceutical gallium compositions, including gallium complexes, that have increased oral bioavailability relative to uncomplexed gallium salts of compounds. The patent also discloses methods for treating conditions and diseases in which inhibition of abnormally increased calcium resorption are desired, including cancer, hypercalcemia, osteoporosis, osteopenia, and Paget's disease.

In addition to the above inventions, there are other patents that claim novel delivery through the oral route (Table 1).

NOVEL DELIVERY SYSTEM ADMINISTERED THROUGH EAR

Minimally Invasive, Sustained, Intra-tympanic Drug Delivery System (Epley, JM) US 7351246

The patent discloses a convenient and preferably wearable system and method for implementing the controlled and sustained delivery of a medical liquid through the tympanic membrane and into the middle ear. The delivery system includes (A) a port structure that produces a minimal opening in the membrane; (B) a wearable and fixated fluid-conduit structure coupleable to the port structure; (C) a reservoir adapted to contain delivery fluid; (D) an operationally controllable pump system applied to the fluid conduit structure; and/or (E) an iontophoretic electrode system applied within the fluid conduit structure and to the subject's body. The system claims to successfully deliver reservoir-held fluid or medically active ions through the fluid conduit and port structures to the middle ear.

Drug Delivery to the Inner Ear and Methods of Using Same (University of Maryland) US 7387614

The patent discloses a method for delivering a pharmaceutical composition (adenoviral vector comprising a polynucleotide encoding for an anti-apoptotic polypeptide and a pancaspase inhibitor) to the inner ear of a mammal without damaging the hearing ability of the subject. The patent describes following steps for such a treatment: (A) visualizing the ear canal; (B) making an incision parallel to the annulus and elevating the tympanic membrane; (C) preserving and identifying the chorda tympani nerve; (D) visualizing the stapes footplate in the ear; (E) drilling a hole in the center of the stapes footplate with a diameter sufficiently large to allow the flow of perilymphatic fluid; (F) injecting about 0.25–10.0 μL of a pharmaceutical composition for treatment of the inner ear of a mammal; and (G) filling the hole in the stapes footplate.

NOVEL DELIVERY SYSTEM ADMINISTERED BY INHALATION ROUTE

Phospholipid-based Powders for Drug Delivery (Weers et al.), US 7442388

The present patent claims the development of phospholipid-based powders for drug delivery through inhalation route. The powders are composed of a polyvalent cation in an amount effective to increase the gel-to-liquid crystal transition temperature of the particle compared to particles without the polyvalent cation. Such hollow and dry porous powders claim to efficiently deliver themselves, active/excipient to the deep lung via the inhalation route. Owing to the increase in gel-to-liquid crystal transition temperature, the formulation claims to possess the advantages of being delivered from a simple passive dry powder inhaler (DPI) device, elimination of the need for the patient to be intubated, better flow properties, improved workability, greater stability on storage, and efficient delivery to the lung due to better dispersibility in the lung periphery.

Table 1. Some patents issued in 2008

Patent/Related Patent No.	Title	Category	Assignee
Targeted Delivery Systems			
7364585	Medical devices comprising drug-loaded capsules for localized drug delivery	Novel targeted drug delivery system	Boston Scientific Scimed, Inc.
7329638	Drug delivery compositions	Novel targeted drug delivery system	Regents of the University of Michigan
7398782	Method for pulmonary drug delivery	Novel targeted delivery system	Portaero, Inc.
7455855	Delivering substance and drug delivery system using the same	Novel targeted delivery system	Santen Pharmaceutical Co., Ltd.
7358226	Ultrasonic concentration of drug delivery capsules	Novel targeted delivery system	Regents of the University of California
7438893	Polybiotin compounds for magnetic resonance imaging and drug delivery	Novel targeted delivery system	Massachusetts General Hospital
7412284, 7395110	Apparatus for electroporation mediated delivery for drugs and genes	Novel device for targeted delivery	Genetronics, Inc.
7385023	Cancer immunotherapy and diagnosis using cytochrome P450 1B1	Novel targeted delivery system	University of Boston; Dana Farber Cancer Institute Inc.
7452857	Methods of treating irritable bowel syndrome and other disorders caused by small intestinal bacterial overgrowth	Novel targeted delivery system	Cedars-Sinai Medical Center
7435407	Inhibition of olfactory neurosensory function to treat eating disorders and obesity	Novel targeted delivery system	Compellis Pharmaceuticals
7361338	Methods to inhibit growth of prostate cancer cells	Novel targeted delivery system	Agensys, Inc.
Novel Delivery Systems by Oral Route			
7387791, 7316818	Liposome drug delivery	Oral route	Oradel Medical Ltd.
7425292	Thin film with non-self-aggregating uniform heterogeneity and drug delivery systems made there from	Novel delivery system by oral route	MonoSol Rx, LLC
7419684	System and method for manufacturing oral osmotic drug delivery devices and methods of administering same	Novel device for oral delivery	Reliant Pharmaceuticals, Inc.
Novel Delivery Systems by Transdermal Route			
7371738	Method of transdermal drug delivery using hyaluronic acid nanoparticles	Transdermal route	University of South Florida
7395111	Transdermal delivery system for water-insoluble drugs	Transdermal route	TransPharma Medical Ltd.
7438203	Dermal penetration enhancers and drug delivery systems involving same	Dermal route	Acrux DDS Pty. Ltd.
7456159	Enhanced drug delivery in transdermal systems	Transdermal route	Noven Pharmaceuticals, Inc.
7384998	Transdermal drug delivery device comprising an acrylic block copolymer-based adhesive	Novel device for transdermal delivery	National Starch and Chemical Investment Holding Corporation
7349733	Iontophoretic drug delivery systems	Novel device for transdermal and ocular delivery	Ceramatel, Inc.
7402156	Counter pressure device for ophthalmic drug delivery	Novel device for drug placement in ophthalmic delivery	Alcon, Inc.
Novel Drug Carrier Systems			
RE040480, RE040546	1,3-Propane diol esters and ethers and methods for their use in drug delivery	Novel carrier delivery system for most routes	Scarista Limited
7455858	Compositions and methods for delivery of photosensitive drugs	Novel carrier system	QLT Inc.
7335509, 7361640	Stable lipid-comprising drug delivery complexes and methods for their production	Novel carrier system	University of Pittsburgh
7316811	Multi-arm polypeptide-poly (ethylene glycol) block copolymers as drug delivery vehicles	Novel carrier system	Nektar Therapeutics AL, Corporation
7413752	Composite hydrogel drug delivery systems	Novel carrier system	Incept LLC
7429563	Peptide carrier for drug delivery	Novel carrier system	Board of Trustees of the University of Illinois
7381716, 7455830	Nanoparticles for protein drug delivery	Novel carrier system	GP Medical, Inc. and National Tsing Hua University
Novel Delivery System by Inhalation Route			
7341739, 7348025	Small particle liposome aerosols for delivery of anti-cancer drugs	Inhalation route	Research Development Foundation
7449175	Delivery of erectile dysfunction drugs through an inhalation route	Inhalation route	Alexza Pharmaceuticals, Inc.
Novel Drug Delivery Device			
7341577, 7351239	Implantable drug delivery pump	Novel device	Renishaw PLC

Patent/Related Patent No.	Title	Category	Assignee
7318932, 7396541, 7329413, 7455907, 7390333	Coatings for drug delivery devices comprising hydrolytically stable adducts of poly(ethylene-co-vinyl alcohol) and methods for fabricating the same	Novel device	Advanced Cardiovascular Systems, Inc.
7329241	Drug delivery system for administering an adjustable preset dose	Novel device	Valeant Pharmaceuticals North America
7347854	Method and apparatus for automatically modifying delivery profile of drug delivery system	Novel device	Infusion Systems, LLC
7384413	Drug delivery device	Novel device	Elan Pharma International Limited
7451760	Controlling drug delivery apparatus	Novel device	Respironics (UK) Ltd.
7335186	Patient controlled drug delivery device	Novel device	O'Neil AGB., O'Neil C.
7425210	Drug delivery system for implantable medical device	Novel device	Cardiac Pacemakers, Inc.
7329236	Intra-aortic renal drug delivery catheter	Novel device	FlowMedica, Inc.
7376460	Method and apparatus for skin absorption enhancement and transdermal drug delivery	Novel device	Mattioli Engineering Ltd.
7434312	Method for manufacturing an implantable drug delivery device with peristaltic pump having a retractable roller	Novel device	Medtronic, Inc.
7462175	Devices, systems and methods for treating disorders of the ear, nose, and throat	Novel device	Acclarent, Inc.

Delivery of Sedative-Hypnotics Through an Inhalation Route (Alexza Pharmaceuticals, Inc.) US 7445768

The current patent discloses a method for delivery of sedative-hypnotics through an inhalation route. The disclosed method involves heating (through passage of current through an electrical resistance element; absorption of electromagnetic radiation, exothermic chemical reactions, etc.) of a thin layer of a sedative-hypnotic (such as zaleplon, zolpidem, zopiclone) on a solid support (aluminum foil sheets, silica, etc.) to form a vapor followed by condensation of the vapors by passage of air to produce sedative-hypnotic comprising aerosol. The delivery of the sedative-hypnotic containing aerosols is via an inhalation device that comprises at least three elements: (1) an element for heating sedative-hypnotic containing composition to form vapor; (2) an element allowing the vapor to cool, thereby providing a condensation aerosol; and (3) an element permitting the mammal to inhale the aerosol. The invention claims to have advantages over the oral therapy and can be indicated for conditions of insomnia and also used as an anticonvulsant, anxiolytic, and myorelaxant.

Patent US 7449174 issued to Alexza Pharmaceuticals uses similar technology for the delivery of analgesics such as acetaminophen, orphenadrine, and tramadol. Other patents disclosing novel drug delivery through the inhalation route are listed in Table 1.

NOVEL DELIVERY SYSTEM ADMINISTERED BY TRANSDERMAL/TOPICAL ROUTE

Transdermal Delivery Systems for Dried Particulate or Lyophilized Medication (TransPharma Medical Ltd.) US 7363075 and US 7335377

The delivery of dry lyophilized peptides and polypeptides is claimed, whereby the stratum corneum is ablated in an area under an electrode to form at least one micro-channel on the skin. The ablation is generated by electric energy through the electrode by current flow or by one or more sparks. The dried

polypeptide of up to 10,000 Da is placed on a non-adhesive liner and used as a patch to deliver the polypeptide through the skin.

Patents US 7395111 and US 7415306, also issued to TransPharma, use similar technologies to deliver water-insoluble drugs and hydrophilic antiemetic drugs, respectively.

Method for Inhibiting Decrease in Transdermal Flux by Inhibition of Pathway Closure (Alza Corporation) US 7438926

Transdermal flux through disrupted stratum corneum (ablation, microneedles, etc.) is decreased with time due to the healing of the ablated tissue. This decrease is inhibited by co-delivering the drug agent together with an amount of an anti-healing agent, which prevents the closure of the disrupted pathway. Anti-healing agents claimed include heparin, pentosan polyphosphate, EDTA, sodium chloride, glucose, glycine, osmotic agents, anticoagulants, anti-inflammatory, and agents inhibiting cellular migration.

Transdermal Delivery of Non-steroidal Anti-inflammatory Drugs (Acrux DDS Pty. Ltd.) US 7387789

A drug delivery system is described comprising (A) a non-steroidal anti-inflammatory, such as ibuprofen; (B) at least one dermal penetration enhancer that is safe skin-tolerant ester sunscreen; and (C) at least one volatile liquid. After application, as the volatile liquid evaporates, the non-volatile composition is rapidly driven into the skin, and the skin area becomes touch dry, preferably within one minute. The skin application area is between 10 and 200 cm², and the volatile liquids claimed include ethanol and isopropanol.

Method and Apparatus for Skin Absorption Enhancement and Transdermal Drug Delivery (Mattioli Engineering Ltd.) US 7376460

A method and apparatus are described for providing a substance to be absorbed into the surface of a patient's skin, such substance being delivered by a probe head, which can provide at the same time (A) bursts of electrical pulses to the skin surface and (B) vibrations to the skin surface. The vibrations are applied at the same frequency rate, a first harmonic or a second harmonic of the same frequency rate, as the burst rate of the electrical pulses.

Method of Enhancing Electrotransport Polypeptide Flux by Amino Acid Substitution with Histidine (Alza Corporation) US 7324846

A method of modifying polypeptide drugs to enhance their transdermal electrotransport flux is described. The modification relates to the substitution of a histidine residue for one or more glutamine, threonine, or asparagine residues. A human growth hormone-releasing hormone analog is claimed, which is modified by replacing at least one glutamine residue at position 16, 30, 31, or 36 in the parent compound with a histidine residue.

Transdermal Drug Delivery Patch System, Method of Making Same, and Method of Using Same (Altea Therapeutics Corporation) US 7392080

A method is claimed for delivering a drug to a patient, comprising (A) contacting the interface layer of a poration device to tissue, said interface layer containing heated probe elements configured to cause ablation of the skin; (B) actuating the poration device to cause at least one pore in the skin; and (C) removing the poration device and applying a reservoir patch onto the microporated area.

Microencapsulated Heat Delivery Vehicles (Kimberly-Clark Worldwide, Inc.) US 7442439

The present patent discloses microencapsulated delivery vehicles comprising an active agent. The microencapsulated heat delivery vehicles include a core composition comprising a matrix material (mineral oil, optionally a surfactant, hydrophobic wax material) and a heating agent (magnesium chloride, calcium chloride). The heating agent in matrix is encapsulated in a thin capsule and is surrounded by one or more moisture protective layers and/or fugitive layers. The patent claims that when the microencapsulated heat delivery vehicles contact wet wipes, heating agent (including other excipients) present in the capsule rupture, releasing heat to cause a warming sensation on the skin. The patent also claims that numerous active ingredients, such as cooling agents and biocides, can also be incorporated into a microencapsulated delivery vehicle.

Other patents describing novel drug delivery systems through the transdermal/dermal route are listed in Table 1.

NOVEL DELIVERY SYSTEM BY PARENTERAL ROUTE

Pharmaceutical Formulation Comprising a Peptide Angiogenesis Inhibitor (Abbott Laboratories Inc.) US 7432245

The patent discloses parenteral formulations of peptides that are useful for sustained release and the methods involved in preparation of the formulations. The patent claims that the new peptide formulation inhibits angiogenesis, and its sustained release profile avoids the need for repeated administration of the medicament and improves therapeutic efficacy due to its prolonged presence *in vivo*. The disclosed formulation in the invention comprises therapeutic amounts of N-Ac-Gly-Val-D-alloIle-Ser-Gln-Ile-Arg-ProNHCH.sub.2CH.sub.3 or its pharmaceutically acceptable salt (such as acetate, pivalate, valproate, and octanoate), poly(lactide-co-glycolide), and an organic solvent.

PATENT RELATED TO NOVEL MEDICAL DEVICES AND PROCESSES

System and Process for Providing at Least One Opening in Dosage Forms (McNeil-PPC, Inc.) US 7404708

The patent discloses apparatus, methods, and processes for making solid dosage forms comprising at least one active ingredient, a core and shell configuration, wherein the shell comprises a hardenable material, such as a thermal-gelling polymer (gelatin), and the shell is provided with at least one opening. The opening(s) are formed while the shell is still in a softened state. The patent states that the system comprises (A) a shell-forming module (for overcoating at least a portion of the core with a soft shell); (B) a post-coating transfer module (for conveying a soft dosage form from the shell-forming module); (C) a punch assembly (for producing at least one opening in the shell); and (D) a hardening module. The process is designed in a fashion that the hardening module is equipped with at least one dryer unit and the punch assembly is located after the shell-forming module but before entering the dryer unit. The post-coating transfer module in the system has a substrate velocity modifying means that ensures controlled transfer of individual substrates between two unit operations that convey individual substrates at different velocities. The invention is advantageous due to its capability of providing openings through outer coatings made of gelatin that cannot be ablated using lasers due to scorching. The patent claims that the ability to form openings by punching while the gelatin is still in a hydrated (soft and deformable) state allows for both an easier punch through and some smoothing of the edges of the punched opening due to cold flow.

Drug Delivery Systems, Kits, and Methods for Administering Zotarolimus and Paclitaxel to Blood Vessel Lumens (Abbott Laboratories) US 7378105

The current patent describes a system in the form of a stent containing zotarolimus (rapamycin analog) and paclitaxel that claims to reduce intimal hyperplasia when implanted in a lumen of a blood vessel of a subject compared to a control system. The patent states that stents included in such a system can be active eluting stents (polymer and drug) or drug-coated stents. The

patent claims that the invention is not restricted to one therapeutic agent or excipient and can include a variety of therapeutic agents and excipients. The patent also states that the supporting structures for the medical devices that are suitable for use in this invention include, but are not limited to, coronary stents, peripheral stents, catheters, arterio-venous grafts, by-pass grafts, and drug delivery balloons used in the vasculature. The patent mentions that the compositions and systems in this invention can be used in combination with other categories of drugs, such as anti-proliferative agents, anti-platelet agents, anti-inflammatory agents, anti-thrombotic agents, cytotoxic drugs, agents that inhibit cytokine or chemokine binding, cell differentiation inhibitors, anti-lipidemic agents, matrix metalloproteinase inhibitors, cytostatic drugs, or combinations.

Method to Enhance Drug Release from a Drug-Releasing Material (Bioretac, Ltd.), US 7419681

The present invention discloses a method of enhancing the drug release rate from a composite material. The patent describes the composite material as a synthetic, bioabsorbable polymer matrix with a drug particle phase dispersed therein, and the release rate of the drug from the polymer matrix is enhanced by orienting the composite material. The patent states that the method comprises deforming the composite material at a temperature above the glass transition temperature of the bioabsorbable polymer matrix to form an oriented composite material. The patent claims that the oriented composite material showed a higher drug release rate than a non-oriented composite material comprising the same bioabsorbable polymer matrix and the same drug as the oriented composite material. The patent states the difference between the non-oriented and oriented composite materials is that the oriented composite material undergoes a solid-state deformation process that is absent in the non-oriented composite material.

Infusion Medium Delivery System, Device and Method with Needle Inserter and Needle Inserter Device and Method (Medtronic Minimed, Inc.) US 7455663

The patent claims the development of an infusion medium delivery system, device, and method that will deliver an infusion medium to a patient-user. The patent discusses a needle inserter device and method for inserting a needle and/or cannula into a patient-user to convey the infusion medium to the patient-user. The patent claims that the system is designed in such a manner that the needle inserter device inserts a needle and cannula into a patient-user's skin and automatically withdraws the needle from the patient-user, leaving the cannula in place and in fluid flow communication with a reservoir. The patent states that the delivery device includes a base portion and a durable portion that is connected to the base portion, and there is provision in the system wherein the base portion can be separated from the durable portion and disposed of after one or more specified number of uses. The base portion provides support to the reservoir and the needle inserter device, while the durable portion supports a drive device for selectively driving the infusion medium out of the reservoir and into the needle and/or cannula.

Method of Using an Expandable Vein Ligator Catheter Having Multiple Electrode Leads (VNUS Medical Technologies, Inc.) US 7406970

The patent discloses a system containing a catheter with a plurality of primary leads to deliver energy for ligating a hollow anatomical structure. The system is designed in such a manner that each of the primary leads includes an electrode located at the working end of the catheter. The primary lead is separated so that each one can receive individually power of a selected polarity. The primary leads are designed to expand outwardly to place the electrodes into apposition with an anatomical structure. The system involves application of high-frequency energy that creates a heating effect in the surrounding tissue of the anatomical structure that further provides reduction in the diameter of the hollow anatomical structure with movements of electrodes close together. The patent states that in case of a hollow structure such as a vein, energy is applied until the diameter of the vein is reduced to the point where the vein is occluded. The system may have a secondary lead surrounding the primary leads that extend beyond the primary leads and have a polarity opposite to the polarity of the primary. The patent states that the polarity of the leads can be switched, and the catheter can be moved during treatment to ligate an extended length of the vein. The catheter in the system can include a lumen to accommodate a guide wire or to allow fluid delivery.

System Method and Apparatus for Localized Heating of Tissue (Apsara Medical Corporation) US 7447550

The patent describes a method, system, and apparatus for precisely performing *in situ* elevation of the temperature of a target tissue volume. The method involves placement of an untethered temperature sensor implant within or adjacent to the target tissue volume, using minimally invasive procedures. The method may also involve use of intraoperatively implanted sensors subsequent to surgery. Implants in the claimed system may be in the form of a single macroscopic device (e.g., wire-shaped implant), multiple macroscopic devices (e.g., wire-shaped implants), and/or multiple microscopic devices (e.g., devices in particulate form that can be injected into a volume of the tissue or attach preferentially systemic injection using chemical binding targeting modalities such as is possible with monoclonal antibody vehicles). Positioning of macroscopic implants may be carried out utilizing an implant instrument somewhat resembling a hypodermic needle. *In situ* heating is performed using conventional non-invasive alternating current field-based devices (RF heating, inductive heating, microwave-based procedures, and ultrasound). The temperature sensor in the implant is formed of a ferromagnetic material that experiences an abrupt magnetic permeability state change at a Curie temperature selected to correspond with the determined thermotherapy set-point temperature. The patent claims that the system has the potential to detect the permeability state transition externally of the body of the patient by monitoring a magnetic field extending through the position of the implant through a magnetometer. The system is designed for thermotherapy endeavors such as an *in vivo*

induction of heat shock proteins, which has important utility in the treatment of cancer, infectious diseases, and other therapies. The patent claims that the implant can be combined with an intra-luminal stent that provides a non-invasive, repeatable, and accurate hyperthermia therapy for restenosis.

Oxygen Enhancing Membrane Systems for Implantable Devices (Dexcom, Inc.) US 7379765

The patent describes systems and methods for increasing oxygen availability to implantable devices. The system includes a membrane configured to provide protection of the implantable device from the biological environment and/or a catalyst for enabling an enzymatic reaction. The membrane system in the invention is made of a polymer formed from a high oxygen-soluble material and is placed adjacent to an oxygen-utilizing source on the implantable device so as to dynamically retain high-oxygen availability to the oxygen-utilizing source during oxygen deficits. The patent claims that such membrane systems are useful for implantable devices with oxygen-utilizing sources and/or in devices that function in low-oxygen environments, such as enzyme-based electrochemical sensors and cell transplantation devices.

Devices, Systems and Methods for Acute or Chronic Delivery of Substances or Apparatus to Extravascular Treatment Sites (Medtronic Vascular, Inc.) US 7357794

The present invention provides transluminal methods and apparatus for delivery of substances (e.g., drugs or other therapeutic or diagnostic agents) or articles (e.g., devices, apparatus, wires, sensors, thermistors, etc.) to interstitial target sites located outside blood vessels within the body of a human or animal patient. The method involves insertion of a vessel wall-penetrating catheter into the vasculature, positioned and oriented within a blood vessel near the target extravascular site, followed by moving a penetrator from the catheter so as to penetrate outwardly through the wall of the blood vessel in the direction of the target site. This is followed by passing of the delivery catheter through a lumen of the penetrator to the target site. A desired substance or apparatus is then delivered to the target site. The patent states that in certain cases, the penetrator may be retracted into the vessel wall-penetrating catheter, and the vessel wall-penetrating catheter may be removed, leaving the delivery catheter in place for chronic or continuous delivery of substance(s) to the target site. The patent states that system may also be designed in such a way that a delivery catheter having an occlusion member or balloon may be advanced into a vein or venule, and the occlusion member or balloon may be used to occlude the lumen of the vein or venule during and after injection of a substance through the catheter, such that the substance will not be carried away by normal venous blood flow and will remain in the vein or venule for a sufficient period of time to have its intended effect (e.g., to enter adjacent tissues through capillary beds drained by that vein or venule).

Coated Implantable Medical Device (Cook Inc. and MED Institute, Inc.) US 7445628

The patent includes methods for making coated implantable medical devices like vascular stents. The methods involve placement of a first coating layer comprising a bioactive material on at least a portion of the coating layer. This is followed by a second porous coating layer with adequate thickness to achieve controlled release of the active. The invention may contain a variety of bioactives, such as chimeric monoclonal antibodies (e.g., an antiplatelet GP IIb/IIIa antibody), antiplatelet/antithrombotic agents, anti-inflammatory steroids, vasodilators, antihypertensives, antimicrobials or antibiotics, antimetotics, antiproliferatives, antisecretory agents, non-steroidal anti-inflammatory drugs, immunosuppressive agents, growth factors and growth factor antagonists, antitumor and/or chemotherapeutic agents, antipolymerases, antiviral agents, photodynamic therapy agents, antibody targeted therapy agents, prodrugs, sex hormones, free-radical scavengers, antioxidants, biologic agents, radiotherapeutic agents, radiopaque agents, and radiolabeled agents.

Trans-septal Intra-cardiac Lead System (Pacesetter, Inc.) US 7340288

The patent describes an apparatus and method of measuring pressure through a septal wall in a patient's heart. The method involves insertion of a lead inserted into the right side of a heart that is then routed through the septum to gain access to the left side of the heart. The lead not only includes an attachment structure to secure the lead to one or both of the septal walls, but also has one or more sensors for measuring cardiac pressure on the left and right sides of the heart. The attachment structure may include at least one protruding tine, membrane, inflatable balloon, involuted spiral or J-lead that engages one or more sides of the septum. The lead may also include a structure (e.g., a spring) to incline the attachment structure against the walls of the septum to automatically adjust the lead to the thickness of the septal wall.

Drug-Eluting Stents Coated with P2Y.sub.12 Receptor Antagonist Compound (Inspire Pharmaceuticals, Inc.) US 7452870

The patent describes a stent coated with one or more P2Y.sub.12 receptor antagonist compounds (in the form of acceptable salt, solvate, or hydrate) for preventing or treating diseases or conditions associated with platelet aggregation and/or platelet activation (venous thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, unstable angina, myocardial infarction, stroke, cerebral embolism, kidney embolisms and pulmonary embolisms, etc.). The patent claims that once the stent is placed in a narrowed or damaged arterial vessel, a therapeutically effective amount of the P2Y.sub.12 receptor antagonist compound is eluted continuously from the stent to the local environment of the stent. The patent states the P2Y.sub.12 receptor antagonist compound-eluting stents show utility in preventing thrombosis and restenosis and are effective in inhibiting the contraction of vascular smooth muscle cells, inhibiting cell proliferation, and reducing inflammation. Several inventions pertaining to novel drug delivery devices, methods, and processes disclosed in 2008 are depicted in Table 1.

NOVEL TARGETED DELIVERY SYSTEMS

Compositions and Methods for Tumor-Targeted Delivery of Effector Molecules (Vion Pharmaceuticals, Inc.) US 7452531

The present patent discloses the preparation and use of attenuated tumor-targeted bacteria (e.g., *Salmonella* or any prokaryotic or eukaryotic cell) vectors for the localized delivery of one or more primary effector molecule(s) (such as TNF cytokine family, anti-angiogenic factors, and cytotoxic polypeptides or peptides) to the site of a solid tumor. The patent claims that the primary effector molecule(s) encoded in the vector has the potential to treat a solid-tumor cancer such as a carcinoma, melanoma, lymphoma, or sarcoma. The patent claims that the attenuated tumor-targeted invention shows reduced toxicity and reduced immunological complications to the host. The patent also states that the novel system delivers secondary effector molecules that may be delivered by the attenuated tumor-targeted bacteria in conjunction with the primary effector molecule(s).

Compositions and Methods of Use of Targeting Peptides Against Placenta and Adipose Tissues (Board of Regents, the University of Texas System) US 7452964

The patent claims compositions and methods for identification and use of peptides for targeting placenta or adipose tissue. The patent states the targeting peptides comprising a contiguous sequence of amino acids specific to target organ, cell, and tissue type are enclosed in a phage that is genetically engineered to express a multitude of such targeting peptides. The patent states that the peptides in the invention may be attached to various therapeutic agents (such as chemotherapeutic agents and proapoptotic peptides) for delivery to receptors located in target tissue. The patent claims that adipose-targeting peptides bind to selective moieties on adipose receptors (such as prohibitin receptor protein complex) and may be used in methods for weight control, inducing weight loss, and treating lipodystrophy syndrome. The patent also claims that the placenta-targeting peptides have the potential to bind to placental receptors (e.g., FcRn/ β 2M), and this behavior may be used to interfere with pregnancy, induce labor, identify potential teratogens (usually compounds binding to placenta receptors), and/or for targeting therapeutic agents to placenta and/or fetus.

Polyamine Compounds and Compositions for Use in Conjunction with Cancer Therapy (Wisconsin Alumni Research Foundation) US 7414154

The patent discloses novel polyamine compounds and pharmaceutical compositions containing one or more chemoprotective polyamine compounds for administration in conjunction with cancer chemotherapy and radiation therapy. The compounds are delivered locally/topically to mucosal or epithelial cells through vehicles (such as emulsions, liposomes, biodegradable microparticles, oils, alcoholic mixtures) to provide protection against the adverse side-effects of chemotherapy radiation therapy, such as alopecia, mucositis, and dermatitis.

Methods of Neurostimulating Targeted Neural Tissue (Spinal Modulation, Inc. and Board of Trustees of Leland Stanford Junior University) US 7447546

The patent describes the method of neurostimulating targeted neural tissues through stimulation systems and components for selective stimulation with or without a pharmacological agent. The method involves neuromodulation of one or more dorsal root ganglia through implantation of an electrode on, in, or around dorsal root ganglia.

Methods and Compositions for Treating Viral Infections Using Antibodies and Immunoconjugates to Aminophospholipids (Board of Regents, University of Texas System) US 7455833

The patent discloses the role of anionic phospholipids and aminophospholipids in tumor vasculature and in viral entry and spread. The patent further provides a number of preferred antibody, immunoconjugate, and duramycin-based compositions that bind and inhibit aminophospholipids and anionic phospholipids for use in the treatment of cancer, viral infections, and related diseases. The patent states that the composition for treatment for viral infections can be delivered intravenously or through aerosol.

Attenuated Rabies Virus with Nucleoprotein Mutation at the Phosphorylation Site for Vaccination Against Rabies and Gene Therapy in the CNS (University of Georgia Research Foundation, Inc.) US 7419816

The current patent claims development of a system containing a mutant virus with mutation at a phosphorylation site in one or more viral proteins that attenuate the virus, leading to improved vaccination potency against rabies. The invention also relates to methods of inducing an immune response (via intact mutant virus and viral proteins) and protecting mammals from infection by rabies virus (by production of antibodies against intact mutant virus and against mutant viral proteins). The patent also includes vectors suitable for delivering a gene to a human or animal cell.

FGF-8 Methods of Use (Auckland Uniservices Limited) US 7414019

The patent discloses a method for treating a bone condition that includes administering an effective amount of fibroblasts growth factor-8 (FGF-8), FGF-8 analog, or a FGF-8 agonist to the patient. The patent claims that administration of FGF-8, FGF-8 analogs, or FGF-8 agonists can be used for treating bone conditions such as osteoporosis, osteopenia, bone defects, or osteogenesis imperfect by stimulating osteoblast growth or modulating osteoblast apoptosis.

Compositions Comprising a Lung Tumor Antigen (Corixa Corporation) US 7425607

The patent claims compositions and methods for the therapy and diagnosis of cancer, specifically lung cancer. The patent discloses the pharmaceutical compositions comprising one or more lung tumor polypeptides, immunogenic portions (polynucleotides that

Table 2. Some patents related to invention of novel compounds with their respective pharmacological activity

Patent No.	Assignee	Chemical Class	Pharmacological Activity
7465741	Janssen Pharmaceutica N.V.	C-Substituted tricyclic isoxazoline derivatives	Anti-depressants
7384950	AstraZeneca AB	Thienopyrimidinediones	Modulation of autoimmune disease
7423182	University of Florida	Aminated polyamines	Carrier molecule
7414131	Renovis, Inc.	Bicycloheteroarylamine compounds	Anti-inflammatory/analgesics
7456194	Bristol-Myers Squibb Company	Pyrazolopurine-based tricyclic compounds	Anti-inflammatory
7419986	Wyeth	Azaheterocyclylmethyl derivatives of heterocycle-fused benzodioxans	Anti-depressants
7323567	Boehringer Ingelheim	–	Respiratory syncytial virus inhibitors
7351704, 7399862	Theravance, Inc.	Indazole-carboxamide derivatives, quinolinone-carboxamide	5-HT _{2A} receptor agonists
7354921	Schering Corporation	Pyrazolotriazines derivatives	Kinase inhibitors
7405302	Amira Pharmaceuticals, Inc.	–	5-Lipoxygenase-activating protein (FLAP) inhibitors
7410989, 7410999	University of North Carolina at Chapel Hill and Georgia State University Research Foundation, Inc., Auburn University	–	Treatment of bovine viral diarrhea virus infection and hepatitis C virus (HCV) infection
7390835	Merck and Co., Inc.	Aralkylamines	Treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders
7449458	Rigel Pharmaceuticals, Inc.	Prodrugs of 2,4-pyrimidinediamine compounds	Treatment of autoimmune disease
7465739	Solvay Pharmaceuticals B.V.	Thiophenepyrimidinone compounds	Treatment of steroid hormone-dependent diseases
7414076	Neurochem (International) Limited	–	Treatment of amyloidosis
7314933	Amgen Inc.	Vanilloid receptor ligands	Anti-inflammatory agents

encode such polypeptides), an antigen-presenting cell expressing such polypeptides and T cells (cells specifically expressing such polypeptides), and a physiologically acceptable carrier. The patent claims that the compositions are useful in the diagnosis, prevention, and/or treatment of diseases, particularly lung cancer.

Monoclonal Antibodies and Cell Surface Antigens for the Detection and Treatment of Small Cell Lung Cancer (SCLC) (ImmunoCellular Therapeutics, Ltd.) US 7435415

The patent provides new monoclonal antibodies and binding fragments that recognize and immunoreact with cell surface antigens found on small cell lung cancer (SCLC) cells. The patent claims that antibodies have tumor specificity and are useful for therapy, diagnosis, monitoring, detecting, and imaging of SCLC disease and of patients having SCLC disease. The patent also states antibody-recognized SCLC-specific surface antigens can serve as targets for detecting, diagnosing, inhibiting, or killing SCLC cells.

Use of Specifically Engineered Enzymes to Enhance the Efficacy of Prodrugs (Board of Trustees of the University of Illinois) US 7419811

The patent provides methods for improving performance of prodrugs by specifically engineered enzymes with enhanced activity toward nucleoside analogs used in cancer chemotherapy and delivering the enzymes to specific target cells in a patient. The patent describes the enhanced activity of modified deoxycytidine kinase (dCK) mutants. The patent also provides information about antibody-conjugated enzymes that can be specifically delivered to leukemic blast cells *in vivo* or *ex vivo* due to their ability to recognize cell surface antigen present on the tumor cells and generate a specific immune response against them.

Lytic Peptide Prodrugs (GHC Research Development Corporation) US 7456146

The patent discloses compositions and methods for making a procytotoxin that is a cytotoxic peptide bound to an inactivator via a peptide bond in such a way that the peptide bond is susceptible to cleavage by a targeting-specific protease. The patent describes a cytotoxic peptide in procytotoxin as a pore-forming cytolytic peptide that is rendered non-toxic by neutralizing the charge on amino acids salient to pore assembly and/or by sterically inhibiting formation of the peptide's active conformation. The patent states that in the presence of specific proteases, the inactive peptide or procytotoxin can be activated to assemble into its lytic conformation and selectively destroy a target cell. The procytotoxin may also have a targeting molecule linked to the N- and/or C-terminus of the cytotoxic peptide and at least one lysine residue. At least one lysine of the cytotoxin (or procytotoxin) is bound through its ε-amino group to the γ-carboxyl group of a glutamic acid residue to form an ε-γ peptide bond.

TNP-470 Polymer Conjugates and Use Thereof (Children's Medical Center Corporation) US 7332523

The patent describes conjugates of water-soluble polymers and o(chloroacetyl-carbamoyl) fumagillol (TNP-470) and the use of such conjugates as specific intracellular carriers of TNP-470 into tumor vessels. The polymer used in such conjugates has a preferred molecular weight in the range of 100 Da to 800 kDa, more preferably no greater than 60 kDa and most preferably in the range of 15 to 40 kDa. The patent claims that use of those conjugates lowers the neurotoxicity of TNP-470.

Treatment of Ocular Disorders (Massachusetts Eye and Ear Infirmary) US 7419666

The patent discloses methods for treating an intraocular disorder in a mammal and is based upon the finding that very late antigen-4 (VLA-4) antagonists can be used in the treatment of certain ocular disorders. The method includes administering to the mammal (human) a VLA-4 antagonist (protein/antibody) that binds specifically to VLA-4 (or to a nucleic acid that binds specifically to VLA-4) in an amount sufficient to ameliorate the symptoms of the disorder. The patent states that the VLA-4 antagonist can also interfere with the binding of VLA-4 to its cognate VLA-4 receptor. The patent claims that VLA-4 antagonists are effective in treatment of ocular disorders such as age-related macular degeneration, uveitis syndromes, retinal vasculitis, sarcoidosis, Eales disease, acute retinal necrosis, Vogt Koyanaki Harada syndrome, ocular toxoplasmosis, radiation retinopathy, proliferative vitreoretinopathy, endophthalmitis, ocular glaucomas, retinal artery occlusions, retinal vein occlusions, retinopathy of prematurity, retinitis pigmentosa, familial exudative vitreoretinopathy (FEVR), idiopathic

polypoidal choroidal vasculopathy, epiretinal macular membranes, and cataracts.

Certain other inventions related to novel targeted drug delivery systems are listed in Table 1.

PATENTS RELATED TO NOVEL COMPOUNDS/ POLYMERS

Novel Temperatures and pH Sensitive Copolymers (Agency for Science Technology and Research) US 7316816

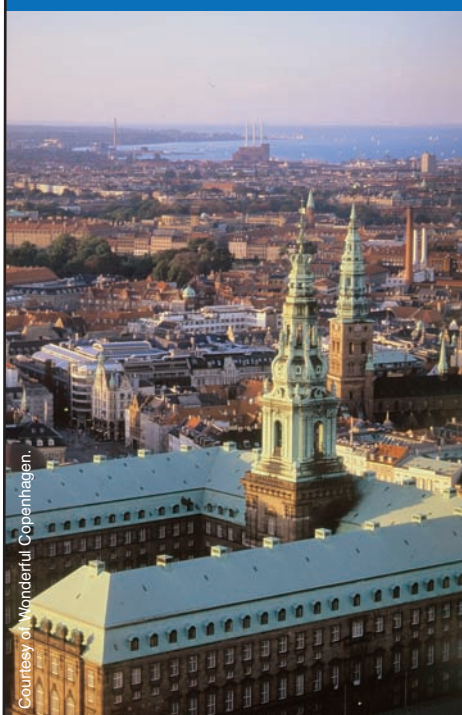
The patent describes a copolymer comprising at least three types of monomeric units: 1) a temperature-sensitive unit; 2) a hydrophilic unit; and 3) a hydrophobic unit comprising at least one pH-sensitive moiety. The patent states that the hydrophobic monomeric unit of the polymer is derived from a copolymerizable unsaturated fatty acid.

Certain patents (Table 2) issued in 2008 disclosed discovery of novel compounds with significant pharmacological activity in treatment of various disorders. ■

CRS Opportunities for You

36th Annual Meeting & Exposition of the Controlled Release Society

July 18–22, 2009 • Bella Center • Copenhagen, Denmark



CRS offers many ways to highlight your company. Take advantage of one or all these opportunities to be heard and seen in Copenhagen. It's easy to do, and you'll be glad you did. Spaces are filling quickly, so act now.

Be Seen In the Capital of Denmark

Reserve your exhibit stand now
Contact Debby Woodard at +1.651.994.3817 today!

For More Exposure For Your Company

Sponsor activities with the CRS
Contact Ronda Thompson at +1.651.994.3836 for more details.

Captivate Your Audience

Submit a Releasing Technology Workshop application by February 27, 2009

Get Up On Your Own Soapbox

Apply before February 27, 2009

www.controlledreleasesociety.org/meeting

In the News

Compiled by Steven Giannos
Industrial Editor

JANUARY 2009

EyeGate Pharma Receives Orphan Drug Designation for Corneal Graft Rejection from U.S. FDA

Market Wire: January 9, 2009 – WALTHAM, Mass. – EyeGate Pharma, the leader in ocular drug delivery, and a specialty pharmaceutical company using iontophoresis technology to safely and non-invasively deliver therapeutics to treat serious ocular diseases, has announced that the U.S. Food and Drug Administration (FDA) has granted Orphan Drug designation for its lead clinical compound, EGP-437 (dexamethasone phosphate), delivered via the EyeGate® II iontophoretic delivery system for the treatment of corneal graft rejection. To date, the U.S. FDA has not approved any product for treating corneal graft rejection.

Stephen From, president and chief executive officer of EyeGate Pharma, commented, “Orphan Drug Designation for our lead compound for treating corneal graft rejection marks an important milestone for the Company. The iontophoretic delivery of dexamethasone phosphate is a more effective means of achieving therapeutic drug levels in the front of the eye than existing therapies, and we look forward to initiating a pivotal trial in this indication during 2009.”

Currently, EyeGate is enrolling two Phase II clinical studies utilizing EGP-437 in uveitis and dry eye patients. The results from these studies are expected in the first half of 2009. The Phase II study in uveitis represents a landmark proof-of-concept study of EGP-437 and EyeGate® II; it is the first-ever U.S. clinical trial under an open IND to employ iontophoresis technology to deliver an active compound into the eye.

Antares Pharma Receives Milestone Payment and Additional Patent Related to Elestrin®

Business Wire: January 6, 2009 – EWING, N.J. – Antares Pharma, Inc. (AMEX: AIS) has announced that the company received a milestone payment of \$450,000 from BioSante Pharmaceuticals, Inc. (NASDAQ: BPAX) related to an agreement with AZUR Pharma for the marketing of Elestrin (estradiol gel) to treat moderate to severe hot flashes in menopausal women in the United States. BioSante received \$3.325 million on signing with AZUR, of which approximately \$1.5 million was purchased inventory. Antares is entitled to 25% of any upfront and milestone payments, as well as a percentage of product royalties. AZUR has agreed to market Elestrin using its women's health and urology sales force of approximately 50 sales people, which targets estrogen-prescribing physicians in the United States, primarily gynecologists.

Elestrin is a low-dose transdermal estradiol therapy delivered in Antares' proprietary advanced transdermal delivery (ATD™) gel system, which is licensed to BioSante. Additionally, Antares is currently conducting a Phase III study of Anturo™, an oxybutynin gel for over-active bladder that incorporates the same ATD™ gel system and was approved in Elestrin by the FDA.

Aegis Therapeutics' Intravail® Technology Selected as Winner in Pharmaceutical Technology's Innovations in Pharma Science Awards for 2008

Business Wire: January 6, 2009 – SAN DIEGO, Calif. – Aegis Therapeutics LLC's Intravail® transmucosal absorption enhancement technology has been selected as a winner in *Pharmaceutical Technology's* Innovations in Pharma Science Awards. Intravail® excipients make it possible to administer previously injectable-only drugs, such as growth hormone, interferon, glucagon, and siRNA drugs, through various non-invasive means, including metered nasal sprays, flash-dissolve buccal tablets, or oral formulations. Intravail® is featured in the December 2008 issue of *Pharmaceutical Technology*. For more information about Aegis, please visit the Aegis website at www.aegisthera.com.

Research from Johns Hopkins University, Department of Pathology, Yields New Findings on Cancer Therapy

NewsRx.com: January 6, 2009 – Data detailed in “*In Vivo* Characterization of a Polymeric Nanoparticle Platform with Potential Oral Drug Delivery Capabilities” have been presented. “Nanotechnology has enabled significant advances in the areas of cancer diagnosis and therapy. The field of drug delivery is a sterling example, with nanoparticles being increasingly used for generating therapeutic formulations of poorly water-soluble, yet potent anticancer drugs,” scientists in the United States reported.

“Whereas a number of nanoparticle-drug combinations are at various stages of preclinical or clinical assessment, the overwhelming majorities of such systems are injectable formulations and are incapable of being partaken orally. The development of an oral nano-delivery system would have distinct advantages for cancer chemotherapy. We report the synthesis and physicochemical characterization of orally bioavailable polymeric nanoparticles composed of N-isopropylacrylamide, methylmethacrylate, and acrylic acid in the molar ratios of 60:20:20 (designated NMA622). Amphiphilic NMA622 nanoparticles show a size distribution of <100 nm (mean diameter of 80 ±34 nm) with low polydispersity and can readily encapsulate a number of poorly water-soluble drugs such as rapamycin within the hydrophobic core. No apparent systemic toxicities are observed in mice receiving as much as 500 mg/kg of the orally administered void NMA622 for 4 weeks. Using NMA622-encapsulated rapamycin (‘nanorapamycin’) as a

prototype for oral nano-drug delivery, we show favorable *in vivo* pharmacokinetics and therapeutic efficacy in a xenograft model of human pancreatic cancer. Oral nanorapamycin leads to robust inhibition of the mammalian target of rapamycin pathway in pancreatic cancer xenografts, which is accompanied by significant growth inhibition ($p < 0.01$) compared with control tumors,” wrote S. Bisht and colleagues, Johns Hopkins University, Department of Pathology.

The researchers concluded, “These data indicate that NMA622 nanoparticles provide a suitable platform for oral delivery of water-insoluble drugs like rapamycin for cancer therapy.” Bisht and colleagues published their study in *Molecular Cancer Therapeutics* (*Molecular Cancer Therapeutics*, 2008;7(12):3878-88).

CyDex Pharmaceuticals Announces CAPTISOL® Technology Used in Recently Approved Cosolvent-free Formulation of Amiodarone IV

Business Wire: January 5, 2009 – LENEXA, Kan. – CyDex Pharmaceuticals, Inc. has announced that Prism Pharmaceuticals’ NEXTERONE®, which recently received new drug application (NDA) approval from the U.S. Food and Drug Administration (FDA), is based on the patent-protected CyDex CAPTISOL® technology platform. NEXTERONE® is the first CyDex proprietary product to achieve the milestone of NDA approval.

CAPTISOL® technology improves the water solubility and stability of active pharmaceutical ingredients. It thereby allowed Prism Pharmaceuticals, Inc. to develop a novel formulation of the antiarrhythmic agent Amiodarone IV (originally marketed as Cordarone® Intravenous) without the cosolvents polysorbate 80 and benzyl alcohol that are used in the innovator product. Cosolvent-free NEXTERONE® addresses the patient care and medication management limitations of conventional intravenous amiodarone in treatment of life-threatening cardiac arrhythmias.

“Prism licensed the worldwide rights to an amiodarone formulation developed with CAPTISOL technology from CyDex in early 2006, and we have worked closely with Prism in providing technical support since then,” stated Theron E. Odlaug, Ph.D., CyDex president and chief executive officer. “Along with our technical support, their success in advancing the product to NDA approval in less than three years further demonstrates the value of CAPTISOL technology in developing novel injectable products that enhance patient treatment in the hospital setting. NEXTERONE’s approval also marks two corporate milestones for CyDex. It is the first of our products formulated in-house to receive FDA approval and, as the fifth product marketed by a CyDex licensing partner, it has the potential to significantly expand our licensing royalty revenue base.” To learn more about the company, please visit www.cydexpharma.com.

Quinnova Pharmaceuticals, Inc. Launches Salvax (Hydrating Topical Foam)

Business Wire: January 5, 2009 – NEWTOWN, Pa. – Quinnova Pharmaceuticals, Inc. has launched Salvax (Hydrating Topical Foam) Rx for the treatment of hyperkeratotic conditions such as psoriasis, keratosis pilaris, and xerosis. Salvax (Hydrating Topical Foam) contains 6% salicylic acid, a potent keratolytic agent, formulated in a water-lipid based foam. The product utilizes Quinnova’s patented Proderm Technology™, which contains a unique combination of physiological lipids, dimethicone, and glycerin that together help to restore the skin barrier, hydrate, and protect the skin, in addition to having anti-inflammatory properties.

Salvax (Hydrating Topical Foam) differs from other topical 6% salicylic acid products (creams or lotions). First and foremost, Salvax (Hydrating Topical Foam) is more than a keratolytic agent that simply removes plaques, scales, and thickened dry skin. Due to the Proderm Technology™, Salvax (Hydrating Topical Foam) also addresses the underlying issues of a compromised skin barrier associated with hyperkeratotic conditions. It repairs and enhances the skin barrier function by replenishing lost lipids, thus resulting in a reduced trans-epidermal water loss (TEWL).

The water-lipid nature of the foam allows the foam ingredients to be rapidly absorbed and incorporated into the outer layers of the skin. Furthermore, the foam provides a cosmetically elegant feel in addition to ease of application because it is non-greasy and spreads easily, especially on hairy regions of the body where the foam does not tangle hair. Unlike some topical foam preparations, Proderm Technology™ does not use either alcohol or other organic solvents, therefore it is well tolerated by patients. The product features and benefits of Salvax (Hydrating Topical Foam) provide added value to treatment efficacy, patient tolerability, and convenience in use, thereby helping to increase compliance and maximize treatment results.

Investigators at KLES College of Pharmacy, Department of Pharmaceutics, Release New Data

NewsRx.com: January 2, 2009 – Researchers detail “*In Vitro* and *In Vivo* Evaluation of Ranitidine Hydrochloride Ethyl Cellulose Floating Microparticles.” According to a study from Belgaum, India, “The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs but also to prolong the presence of dosage forms in the stomach in order to improve the bioavailability of drugs with a ‘narrow absorption window’. In the present study, an anti-ulcer drug, ranitidine hydrochloride, is delivered through a gastroretentive ethyl cellulose-based microparticulate system capable of floating on simulated gastric fluid for >12 h.”

“Preparation of microparticles is done by solvent evaporation technique with modification by using an ethanol co-solvent system. The formulated microspheres were free flowing with good packability and encapsulation efficiencies were up to 96%.

In the News continued from page 43

Scanning electron microscopy confirmed porous, spherical particles in the size range 300-750 micron. Microspheres showed excellent buoyancy and a biphasic controlled release pattern with 12h. *In vivo* bioavailability studies performed on rabbits and T(max), C(max), [and] AUC were calculated and confirmed significant improvement in bioavailability," wrote V. S. Mastiholimath and colleagues, College of Pharmacy, Department of Pharmaceutics.

The researchers concluded, "The data obtained thus suggests that a microparticulate floating delivery system can be successfully designed to give controlled drug delivery, improved oral bioavailability and many other desirable characteristics." Mastiholimath and colleagues published the results of their research in the *Journal of Microencapsulation* (Journal of Microencapsulation, 2008;25(5):307-14).

New Data Reported by M. Ahmed and Co-authors

NewsRx.com: January 2, 2009 – New data are presented in the report "Potential of Nanoemulsions for Intravenous Delivery of Rifampicin." According to recent research from Libya, "The aim of the present study was to develop, characterize and evaluate nanoemulsion formulations for intravenous delivery of rifampicin (RIF). Different oil-in-water (o/w) nanoemulsions were prepared by the aqueous phase titration method."

"Prepared nanoemulsions were subjected to thermodynamic stability tests for phase separation, creaming, cracking, coalescence or phase inversion and dispersibility test[s] for dilution capacity. Nanoemulsion formulations, which passed these tests, were characterized in terms of droplet size, viscosity, entrapment efficiency, homogeneity and pH. The selected formulations were subjected to *in vitro* dissolution studies using a dissolution apparatus-XXIII in dialysis bag. Best results were obtained with the formulation which consisted of 150 mg of RIF, 15% w/w of Sefsol 218, 18.75% w/w of Tween 80, 6.25% w/w of Tween 85 and 60% w/w of normal saline. The optimized formulation was also subjected to stability studies according to the ICH guidelines. The formulation was found to be stable for more than 19 months," wrote M. Ahmed and colleagues.

The researchers concluded, "These results indicated the potential of nanoemulsions for intravenous delivery of RIF." Ahmed and colleagues published their study in *Pharmazie* (Pharmazie, 2008;63(11):806-11).

Scientists at University of KwaZulu-Natal Describe Research in Drug Delivery

NewsRx.com: January 2, 2009 – A new study, "Exploring the Use of Novel Drug Delivery Systems for Antiretroviral Drugs," is now available. "Novel drug delivery systems present an opportunity for formulation scientists to overcome the many challenges associated with antiretroviral (ARV) drug therapy, thereby improving the management of patients with HIV/AIDS. This paper provides a comprehensive review of the various ARV delivery systems that have been developed for achieving sustained drug release kinetics, specifically targeting

drugs to the macrophages, brain and gastric mucosa, and for addressing formulation difficulties such as poor solubility, stability and drug entrapment," scientists in Durban, South Africa reported.

"Studies on the potential of systems for alternative routes of ARV drug administration, i.e., transdermal, buccal and rectal, are also highlighted. The physico-chemical properties and the *in vitro/in vivo* performances of various systems such as sustained release tablets, ceramic implants, nanoparticles, nanocontainers, liposomes, emulsomes, aspasomes, microemulsions, nanopowders and Pheroid™ are summarised. Further studies that remain to be undertaken for formulation optimisation are also identified," wrote E. Ojewole and colleagues, University of KwaZulu-Natal.

The researchers concluded, "This review highlights the significant potential that novel drug delivery systems have for the future effective treatment of HIV/AIDS patients on ARV drug therapy." Ojewole and colleagues published their study in the *European Journal of Pharmaceutics and Biopharmaceutics* (European Journal of Pharmaceutics and Biopharmaceutics, 2008;70(3):697-710).

DECEMBER 2008

Labopharm Announces FDA Approval of Once-Daily RYZOLT™

CNW: December 31, 2008 – LAVAL, Quebec, Canada – Labopharm Inc. (TSX: DDS; NASDAQ: DDSS) has announced that RYZOLT™ (tramadol HCl extended-release tablets), Labopharm's once-daily formulation of the analgesic tramadol, has been approved by the U.S. Food and Drug Administration (FDA). RYZOLT™ is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

"The approval of our first product in the United States is a major milestone for our Company and we look forward to our product's launch in the world's largest market for pain medications," stated James R. Howard-Tripp, president and chief executive officer Labopharm Inc. "We believe that RYZOLT offers physicians and patients an excellent option for the treatment of pain with the benefit of once-daily dosing. We look forward to the launch of our product by our marketing partner for the U.S., Purdue Pharma."

RYZOLT™ is a centrally acting analgesic composed of a dual-matrix delivery system, with both immediate-release and extended-release characteristics. Labopharm's marketing partner for its product in the United States, Purdue Pharma L.P., anticipates launching RYZOLT™ tablets in 100 mg, 200 mg, and 300 mg dosage strengths in the second quarter of 2009.

The approval of RYZOLT™ is the first U.S. FDA approval that Labopharm has obtained for a medication using its patented Contramid® controlled release technology for oral administration of solid-dosage medications. Labopharm believes that its

Contramid® technology can be applied to a wide range of complex, small, highly water-soluble molecules to control their release over a 24-hr period with a desired pharmacokinetic profile.

Data from University of Cincinnati Advance Knowledge in Medical Ultrasound

December 30, 2008 – In a recent article published in the *Journal of Ultrasound in Medicine*, scientists in the United States conducted a study “To achieve ultrasound-controlled drug delivery using echogenic liposomes (ELIPs). Ultrasound-triggered release of hydrophilic and lipophilic agents *in vitro*, using color Doppler ultrasound with a clinical 6-MHz compact linear array transducer, was assessed. Calcein, a hydrophilic agent, and papaverine, a lipophilic agent, were each separately loaded into ELIPs.”

“Calcein-loaded ELIP (C-ELIP) and papaverine-loaded ELIP (P-ELIP) solutions were circulated in a flow model and treated with 6-MHz color Doppler ultrasound or Triton X-100. Treatment with Triton X-100 was used to release the encapsulated calcein or papaverine content completely. The free calcein concentration in the solution was measured directly by spectrofluorimetry. The free papaverine in the solution was separated from liposome-bound papaverine by spin column filtration, and the resulting papaverine concentration was measured directly by absorbance spectrophotometry. Dynamic changes in echogenicity were assessed, with low-output B-mode ultrasound (mechanical index, 0.04) as mean digital intensity. Color Doppler ultrasound caused calcein release from C-ELIPs compared with flow alone ($P < .05$) but did not induce papaverine release from P-ELIPs compared with flow alone ($P > .05$). Triton X-100 completely released liposome-associated calcein and papaverine. Initial echogenicity was higher for C-ELIPs than P-ELIPs. Color Doppler ultrasound and Triton X-100 treatments reduced echogenicity for both C-ELIPs and P-ELIPs ($P < .05$),” wrote J. A. Kopechek and colleagues, University of Cincinnati.

The researchers concluded, “The differential efficiency of ultrasound-mediated pharmaceutical release from ELIPs for water- and lipid-soluble compounds suggests that water-soluble drugs are better candidates for the design and development of ELIP-based ultrasound-controlled drug delivery systems.” Kopechek and colleagues published their study in the *Journal of Ultrasound in Medicine* (Journal of Ultrasound in Medicine, 2008;27(11):1597-1606).

Researchers at Westfälische Wilhelms University Munster Describe Drug Delivery Technology

NewsRx.com: December 26, 2008 – Research findings are discussed in a new report, “Control of Drug Release from Capsules Using High Frequency Energy Transmission Systems.” “In the present investigations new drug delivery systems have been developed, which are controlled by a computer and a high frequency energy transmission system. The capsules consist of a drug reservoir, a high frequency receiver, a gas generating section and a piston to pump a drug solution or drug suspension out of the reservoir,” researchers in Germany reported.

“Mechanical energy is generated inside the capsule through electrolysis, if a 27 MHz high frequency field is in resonance with the receiver inside the capsule. Two different miniaturised oscillatory circuits were constructed, which act as the receivers in the capsules. Tramadol was used in release experiments as a model drug. Delayed and pulsed release profiles were obtained,” wrote R. Gröning and colleagues, Westfälische Wilhelms University Munster.

The researchers concluded, “A computer-controlled system was constructed, in which the programmed release profiles are compared with the actual release of the drug.” Gröning and colleagues published their study in the *International Journal of Pharmaceutics* (International Journal of Pharmaceutics, 2008;364(1):9-13).

New Biomedical Materials Research from Sichuan University Outlined

December 23, 2008 – According to recent research from Chengdu, People’s Republic of China, the synthesis of a biodegradable polyester polymer with hydrophilic polyethylene glycol chains, preparation of DHAQ-loaded nanoparticles from such polymer, and biodistribution of the drug-loaded particles were investigated. “Biodegradable monomethoxy poly(ethylene glycol) poly(lactide-co-glycolide)-monomethoxy poly(ethylene glycol) (MeO-PEG-PLGA-PEG-OMe, PELGE) copolymers were synthesized by ring-opening polymerization as the drug carriers.”

“A double emulsion method with dextran-70 as an emulsifier was employed to prepare the nanoparticles. DHAQ-PELGE nanoparticles and free DHAQ were employed for the *in vivo* biodistribution studies after intravenous administration through the tail veins in mice. At various time intervals, the mice were sacrificed and several organs and tissues harvested, including hearts, livers, spleens, lungs, kidneys, and blood. The DHAQ concentrations in the collected tissues and plasmas were determined using high performance liquid chromatography. The DHAQ concentrations in mice plasmas in the experimental groups were significantly higher than those in the control group and 3.72%, of total administrations dosages (TAD) of these particles with DHAQ remained in circulation even 96 h after intravenous injection. Compared with the free DHAQ, DHAQ-loaded PELGE nanoparticles had longer circulation properties,” wrote Y. R. Duan and colleagues, Sichuan University.

The researchers concluded, “Further research should be done for intravenous injection of this material as drug carriers.” Duan and colleagues published their study, “A Preliminary Study on MeO-PEG-PLGA-PEG-OMe Nanoparticles as Intravenous Carriers” in the *Journal of Biomedical Materials Research Part a* (Journal of Biomedical Materials Research Part a, 2008;87A(2):515-23).

In the News continued from page 45

Positive Phase I Clinical Trial Results for Transdermal Lidocaine

NewsRx.com: December 22, 2008 – Phosphagenics Limited (ASX: POH; OTCQX: PPGNY) has announced the successful completion of a Phase I clinical trial that examined the ability of its patented drug delivery system, TPM, to topically deliver the pain-relief drug, lidocaine, safely into humans. The trial demonstrated that the patented lidocaine formulation was able to deliver a significantly greater amount of lidocaine into the localized area of the skin compared to a leading commercial product.

Lidocaine is a well-known topical anesthetic, sales of which exceeded US\$1.2 billion in 2007. It is used for a wide variety of ailments, including temporary relief of rashes, stings, sprains, strains, bites, and burns. This clinical trial compared the dermal penetration and measured the systemic exposure of lidocaine between one of the leading marketed products, Xylocaine® (5% lidocaine), and Phosphagenics' TPM/lidocaine (5% lidocaine).

One hour after application, TPM/lidocaine delivered 500% more ($P < 0.001$) lidocaine into the stratum corneum, the outer layer of the skin, than the commercial product, Xylocaine®. Phosphagenics' TPM/lidocaine also augmented the depth of penetration, with 450% ($P < 0.01$) more lidocaine found in the deepest layers of the skin sampled.

TPM/lidocaine significantly increased the amount, rate, and depth of lidocaine penetration into the skin compared with Xylocaine®, parameters that are normally expected to produce a local analgesic effect. Despite the increase in dermal drug delivery, TPM/lidocaine did not increase the plasma lidocaine concentration compared with Xylocaine® after 6 hr.

Dr. Esra Ogru, executive vice president of research and development at Phosphagenics stated, "While we have previously demonstrated the penetrative power of our TPM technology, the success of this trial validates the versatility and precision of Phosphagenics' drug delivery platform in humans. We view this as a major achievement for our company and look forward to moving ahead with further clinical trials."

The open-label, single-center study was conducted at the Centre for Pharmaceutical Research, University of South Australia, under the guidance of principal investigator Dr. David Foster. Eleven healthy adult volunteers enrolled in the bioavailability trial of dermal and systemic pharmacokinetics, which incorporated secondary endpoints of safety and tolerability.

Findings from Shenyang Pharmaceutical University Broaden Understanding of Drug Delivery Science and Technology

NewsRx.com: December 19, 2008 – "In order to obtain a hepatotropic-targeting conjugate of the anti-tumor drug, 5-fluorouracil-1-acetic acid (5-FUA) was coupled with poly(asparthydrazide-co-2-hydroxyethyl aspartamide) (PAHy-HEA), and the obtained poly (asparthydrazide-co-2-

hydroxyethyl aspartamide)-5-FUA was reacted with lactobiono-1, 5-lactone to obtain a water-soluble hepatotropic conjugate of 5-FUA, galactosylated poly (asparthydrazide-co-2-hydroxyethyl aspartamide)-5-FUA (gal-PAGy-HEA-5-FUA). The successful preparation of the conjugate was confirmed by DSC, HPLC, FT-IR and UV spectra," scientists in Shenyang, People's Republic of China, reported.

"The drug loading and galactose content of the gal-PAHy-HEA-5-FUA was 11.9% w/w and 18.9% w/w (24.2%mol/mol), respectively. The 5-FUA cumulative release from gal-PAHy-HEA-5-FUA in buffer solutions, plasma and liver homogenate was less than 3%, approximately 9 and 22% within 8 h, respectively. The conjugate was stable in buffer solutions and in plasma, and there was efficient drug release in targeted liver," wrote T. Y. Jiang and colleagues, Shenyang Pharmaceutical University.

The researchers concluded, "In liver, the AUC and maximum concentration of 5-FUA from gal-PAHy-HEA-5-FUA was approximately 18-fold and 6-fold that from free 5-FUA respectively, which showed that the 5-FUA conjugation to gal-PAHy-HEA is a promising strategy to enhance liver-targeting ability." Jiang and colleagues published their study, "The Investigation on a Conjugate of 5-Fluorouracil-1-acetic Acid and Galactosylated Poly (Aspartamide): Synthesis, Stability and Liver Targeting," in the *Journal of Drug Delivery Science and Technology* (Journal of Drug Delivery Science and Technology, 2008;18(4):225-30).

Research from Shenyang Pharmaceutical University in the Area of Drug Delivery Science and Technology Published

NewsRx.com: December 19, 2008 – According to recent research from Shenyang, People's Republic of China, "The purpose of the present study was to investigate the effect of ion-pairing on the permeation of glibenclamide through rat skin. Diethylamine, triethylamine, ethanalamine, diethanolamine and triethanolamine were used as counter-ions."

"The steady-state flux of glibenclamide markedly increased in the presence of counter-ions ($p < 0.05$). These results suggest that it is possible to enhance the permeation of glibenclamide by using an ion-pair approach. Moreover, the extent of enhancement possible depends on the alkalinity, molecular weight, structure of the counter-ions and the dielectric constant of the donor solution. The influence of penetration enhancers on the permeation of glibenclamide was also determined. All the penetration enhancers studied increased the flux of glibenclamide compared with the control," wrote R. Ma and colleagues, Shenyang Pharmaceutical University.

The researchers concluded, "Among these enhancers, menthol and N-methyl-2-pyrrolidone showed the greatest enhancing activity." Ma and colleagues published their study, "Effect of Ion-Pairing on the Permeation of Glibenclamide Through Rat Skin," in the *Journal of Drug Delivery Science and Technology* (Journal of Drug Delivery Science and Technology, 2008;18(4):279-84).

Research from Shenyang Pharmaceutical University Yields New Data on Controlled Release

NewsRx.com: December 19, 2008 – According to a study from Shenyang, People’s Republic of China, “A new type [of] double-layered osmotic pump (DOP) system was developed for the delivery of water insoluble drug bezafibrate with [a] daily dose of 400 mg, polymer was used as drug carrier and alkaline substance was added to the core as solubilizer.”

“This novel DOP was designed as a combination of various osmotic pumps, such as push-pull osmotic pump, elementary osmotic pump and monolithic polymer osmotic pump. Two layers of the osmotic pump system were both drug-containing, the first layer of the DOP was designed using elementary osmotic pump theory which involved 20 mg sodium carbonate to enhance the solubility of model drug, the second layer was designed using monolithic polymer osmotic pump theory by adding 50 mg polyoxyethylene oxide as suspending and swelling agent, and a double layer was designed using monolithic polymer osmotic pump theory by adding 50 mg polyoxyethylene oxide as suspending and swelling agent, and a double layer osmotic pump was formed by the combination of the two layers which could operate as a push-pull osmotic pump,” wrote X. Yang and colleagues, Shenyang Pharmaceutical University.

The researchers concluded, “Orifices with the same diameter at 0.8 mm were drilled on both sides of membrane surfaces and the release profile of drug presented zero-order in 12 h. The results showed that factors that had considerable influence on *in vitro* drug release behavior were: the proportion of bezafibrate in two layers, the amount of polyoxyethylene oxide in core tablets, the percentage of polyethylene glycol in coating materials, the coating level and the orifice.”

Yang and colleagues published the results of their research, “A New Type of Double-Layered Osmotic Pump Controlled Release Tablets of Bezafibrate with Poor Water Solubility and Large Dosage,” in the *Journal of Drug Delivery Science and Technology* (Journal of Drug Delivery Science and Technology, 2008;18(4):273-77).

NeurogesX Announces FDA Acceptance to Review New Drug Application for NGX-4010 to Treat Post-herpetic Neuralgia

PRNewswire-FirstCall: December 19, 2008 – SAN MATEO, Calif. – NeurogesX, Inc. (NASDAQ: NGSX), a biopharmaceutical company focused on developing and commercializing novel pain management therapies, has announced that the U.S. Food and Drug Administration (FDA) has accepted its New Drug Application (NDA) to review its investigational product candidate, NGX-4010, for the management of pain due to post-herpetic neuralgia (PHN). NGX-4010 is a dermal high-concentration capsaicin patch designed to provide rapid, localized, and sustained pain relief in patients with PHN.

The company also announced that it has proposed to market NGX-4010 under the brand name Qutenza™, pending FDA approval of both the NDA and the proposed brand name. The NDA, submitted to the FDA in October 2008, includes data from over 2,300 patients. The application is supported by positive results from two pivotal studies in which a single 60-min application of Qutenza™ demonstrated a statistically significant reduction in pain from baseline for up to 12 weeks in patients with PHN.

Jazz Pharmaceuticals Announces Issuance of Key Patent for Once-a-Day LUVOX CR®

PRNewswire-FirstCall: December 18, 2008 – PALO ALTO, Calif. – Jazz Pharmaceuticals, Inc. (Nasdaq: JAZZ) has announced that the U.S. Patent and Trademark Office has issued U.S. Patent No. 7,465,462 covering its Once-a-Day LUVOX CR® (fluvoxamine maleate) extended-release capsule product. The patent was assigned to Elan Pharma International Limited and is exclusively licensed to Jazz Pharmaceuticals in the United States through a product license agreement with Solvay Pharmaceuticals, Inc. The patent claims the formulation incorporating Elan’s SODAS® (spheroidal oral drug absorption system) technology, as well as a method of using the formulation for the treatment of obsessive compulsive disorder (OCD).

LUVOX CR® was approved on February 28, 2008, by the U.S. Food and Drug Administration (FDA) for the treatment of social anxiety disorder (SAD) and obsessive compulsive disorder (OCD) in adults. The patent has been listed for LUVOX CR® in the FDA Orange Book.

MonoSol Rx Enters Agreement with Hikma Pharmaceuticals PLC for Thin-Film Pharmaceutical Products in the Middle East

PRNewswire: December 16, 2008 – WARREN, N.J. and PORTAGE, Ind. – MonoSol Rx, the developers of PharmFilm® technology and a drug delivery company specializing in dissolving thin-film pharmaceutical products, has entered into an agreement for thin-film pharmaceutical products with Hikma Pharmaceutical PLC (LSE: HIK; DIFX: HIK), a multinational pharmaceutical group focused on developing, manufacturing, and marketing a broad range of generic and in-licensed pharmaceutical products across the Middle East, North Africa, the United States, and Europe.

Under terms of the agreement, Hikma has acquired an exclusive license to distribute in the Middle East three thin-film pharmaceutical products based on MonoSol Rx’s proprietary PharmFilm® delivery technology. Hikma will be responsible for obtaining all registrations and approvals required to market the products throughout the region. MonoSol Rx, which will exclusively supply the thin-film products to Hikma, is eligible to receive milestone payments and payments for the purchase of product supply.

In the News continued from page 47

Mark Schobel, president and CEO of MonoSol Rx, stated, “We are excited to enter an agreement with Hikma that extends the geographic foothold of our proprietary PharmFilm technology. As a leading pharmaceutical company serving the Middle Eastern markets, we are confident in Hikma’s ability to secure regulatory approvals and effectively sell three important thin film product formulations throughout the territory. In addition to expanding our reach into new geographic territories, our partnership with Hikma further validates our proprietary PharmFilm technology, leadership in thin film drug development, and growing intellectual property portfolio.”

Said Darwazah, chief executive officer of Hikma Pharmaceuticals PLC, said, “Our collaboration with MonoSol Rx is an excellent opportunity for us to offer differentiated thin film products throughout the Middle East. We expect to leverage our experience with the regulatory landscape along with our commercial capabilities to secure approvals and successfully market each of the thin film products supplied by MonoSol Rx.”

AAIPharma and CORTRIA Corporation Sign Drug Delivery Deal

NewsRx.com: December 15, 2009 – AAIPharma and CORTRIA Corporation have signed a deal granting CORTRIA Corporation the right to use AAIPharma’s proprietary, controlled release oral drug delivery technology known as ProCR™ in conjunction with CORTRIA’s TRIA-662 drug candidate.

ProCR™ is a novel controlled release technology developed by AAIPharma for use with orally administered drug products and reflects AAIPharma’s long-standing commitment to providing safe, cost-effective, and easy-to-manufacture formulation offerings. TRIA-662 is CORTRIA’s lead drug candidate currently in Phase II clinical development for dyslipidemia. In preliminary human studies, TRIA-662 has shown the potential to provide benefits for niacin therapy without causing skin flushing, a common, use-limiting side effect of niacin agents.

“We believe TRIA-662 is one of the most exciting drug candidates in the cardiovascular pipeline today and we are pleased to work with CORTRIA to help develop this product candidate for patients with dyslipidemia,” said Lee Karras, senior vice president of global pharmaceutical services at AAIPharma. “Our goal is to work with companies like CORTRIA who have best-in-class therapeutic candidates and who can further benefit from best-in-class oral drug delivery solutions to maximize therapeutic performance.”

“AAIPharma has a rich history of providing oral solid dosage formulation development and has already been an outstanding partner for CORTRIA in the area of analytical services,” commented Daniel Grau, CEO and vice chair of CORTRIA. “Through this new agreement, we look forward to expanding our relationship with AAIPharma by applying its ProCR™ technology in the development of commercial formulations of TRIA-662.”

Midatech Group and MonoSol Rx Enter Collaboration Agreement to Unite Nanoparticle and Thin-Film Drug Delivery Technologies

NewsRx.com: December 12, 2008 – Midatech Group, a world leader in the production and application of synthetically produced nanoparticles, and MonoSol Rx, the developers of PharmFilm® technology and a drug delivery company specializing in dissolving thin-film pharmaceutical products, have announced a partnership to develop new drug formulations combining biocompatible nanoparticles and PharmFilm® delivery technologies.

Under the terms of the agreement, Midatech Ltd. and MonoSol Rx will jointly research, develop, and commercialize new drug candidates designed to deliver therapeutic nanoparticles in thin film. Research and development will occur at Midatech Biogune S.L., in Bilbao, Spain, with clinical development at a new facility in Basel, Switzerland. MonoSol Rx’s facility in Portage, IN, is critical in these joint activities. Further terms were not disclosed.

Prof. Tom Rademacher, chair of Midatech Group, commented, “MonoSol Rx’s PharmFilm® technology provides an ideal platform for us to evaluate clinical applications for our biocompatible nanoparticle technology. The ability of PharmFilm® to carry highly uniform low doses of nanoparticles makes it well-suited to deliver our biocompatible nanoparticles sublingually, buccally or through traditional intragastric delivery. We look forward to working with MonoSol Rx to develop groundbreaking pharmaceutical products.”

A. Mark Schobel, president and CEO of MonoSol Rx, stated, “Our collaboration with Midatech provides us with an exciting entry into the emerging field of nanomedicine. The size and chemical composition of Midatech’s biocompatible nanoparticles are ideally suited for delivery using our PharmFilm® technology, and should provide another avenue for us to extend the commercial potential of new and currently marketed drugs. The combination of these two complementary and well-matched technologies offers a unique opportunity to move beyond the limitations of traditional delivery formulations to create new and compelling drug candidates with the potential for greater convenience, efficacy at lower doses, and faster onset of action. Most importantly, the mating of MonoSol Rx’s and Midatech’s technologies will enable the oral delivery of many challenging drugs that up to now could not be delivered orally.”

Midatech’s biocompatible nanoparticles possess a number of unique properties ideal for therapeutics, diagnostics, and other enabling applications. Among its attributes, Midatech’s nanoparticles are water soluble; can present multiple ligands, allowing for multivalent drug or multi-drug delivery on a single particle; and can be delivered via different routes of administration due to their size and stability to enzymatic digestion.

3M Licenses Dry Powder Inhaler Technology from Cambridge Consultants

Business Wire: December 10, 2008 – ST. PAUL, Minn. – 3M Drug Delivery Systems has announced the signing of an exclusive technology license and purchase agreement with Cambridge Consultants for its Conix™ dry powder inhaler (DPI) technology platform. The Conix DPI technology, also called reverse-flow cyclone technology, adds to 3M's extensive inhalation technology platform.

"This new technology platform enhances 3M's capability to provide partner pharmaceutical and biotechnology companies with innovative drug delivery solutions," said James Vaughan, division vice president, 3M Drug Delivery Systems Division. "We believe the Conix technology will add to the breadth of our unique inhalation technology portfolio and enables us to offer new and exciting drug delivery alternatives."

The Conix™ technology platform includes a variety of inhaler types, ranging from a single-dose device suitable for applications such as immunizations, to a multi-unit dose suitable for routine therapies, such as asthma and COPD.

Emisphere Announces Reorganization Plan to Strengthen Financials and Focus on Technology Application

Globe Newswire: December 8, 2008 – CEDAR KNOLLS, N.J. – Emisphere Technologies, Inc. (Nasdaq: EMIS), a biopharmaceutical company that focuses on an improved delivery of therapeutic molecules using its Eligen® technology, has announced plans to strengthen its financial foundation, bolster its long-term prospects, and maintain its focus on advancing and commercializing its Eligen® technology. These plans will allow Emisphere to continue with its current programs while reducing its cash burn rate by over 60% from current levels.

"The product pipeline and the value of the Company and its technology have been overshadowed by the issues in the financial markets that many companies are facing today," stated Michael V. Novinski, president and chief executive officer of Emisphere. Currently, Emisphere has two products in Phase III for osteoporosis and osteoarthritis with its partner, Novartis AG. Plans are also in place to commercialize the technology by applying it to vitamin B₁₂, thereby addressing problems with oral supplementation of this critical vitamin. Also, a new early-stage partnership was announced with Novo Nordisk for the treatment of Type 2 diabetes and the oral administration of GLP-1 analogues. Finally, the company also has announced encouraging data on an oral formulation of PTH with its partner Novartis AG.

Effective January 1, 2009, Emisphere will adopt a business model that uses third-party contractors more so than in the past. The company will maintain and utilize its scientific expertise in chemistry, process chemistry, applied biology, formulation, and animal testing, as well as commercial and business development. Outside resources, under the supervision of Emisphere staff, will be used for tasks as they relate to the requests of existing and potential partners rather than maintaining these facilities

internally. The company, which has over 4,000 proprietary carriers in its Eligen® carrier library, will focus on existing and new partnerships and applying the technology to new molecules and nutrients.

Alkermes Initiates Clinical Trial for ALKS 33, a Novel Oral Molecule with Potential Benefits in Addiction and Other CNS Disorders

Business Wire: December 4, 2008 – CAMBRIDGE, Mass. – Alkermes, Inc. (NASDAQ: ALKS) has announced the initiation of a Phase I study of ALKS 33, an oral opioid modulator for the potential treatment of addiction and other central nervous system (CNS) disorders. ALKS 33 is the company's first novel, small-molecule drug candidate to enter the clinic. The molecule builds on Alkermes' scientific expertise in brain reward pathways, as well as the company's clinical and commercial knowledge in the field of addiction. In addition, Alkermes has initiated a clinical pharmacokinetic study to further explore ALKS 29, a potential oral treatment for alcohol dependence.

"The progress of these two candidates clearly demonstrates our commitment to building a commercial enterprise with promising prospects for growth," said David Broecker, president and CEO of Alkermes. "The combination of our strong financial health, the success of two commercial products and our proven science puts Alkermes in a unique position to create new proprietary product opportunities that have the potential to help address the needs of a broad range of patients."

The development of these two candidates further underscores the significant expertise in and commitment to the area of addiction at Alkermes. VIVITROL®, the company's first commercial product in addiction, is currently approved for the treatment of alcohol dependence in the United States and Russia. VIVITROL® is the only once-monthly injectable medication approved for the treatment of alcohol dependence.

NanoVector to Commercialize First Biologic Nanoparticle Drug Delivery System

Business Wire: December 2, 2008 – RALEIGH, N.C. – NanoVector, Inc. has licensed the plant virus nanoparticle drug delivery system developed by Profs. Stefan Franzen and Steven Lommel from North Carolina State University. "This is breakaway technology that will finally provide the highly sought after selective targeting of tumors and intracellular delivery of anti-cancer agents for improved efficacy and fewer unpleasant side effects," said Albert Bender, Ph.D., NanoVector CEO. "The plant virus nanoparticle has evolved over millions of years to have several inherent characteristics essential for a successful nanoparticle delivery system and [is] superior to any chemistry based nanoparticle designed and engineered by humans," continued Dr. Bender.

The most important property of the virus is its built-in sensor-actuator system. When the virus carrying the therapeutic agent enters a cell, it senses a change in chemical environment and

In the News continued from page 49

automatically unloads its cargo. Therefore, the highly toxic therapeutic agent is released only in a cell, never in the blood stream, as with manmade particles that depend on capsule degradation or require an external trigger to open the particles for the release of their content. The benefit derived from this feature of the NanoVector nanoparticle is the minimization of the toxic side effects associated with free anti-cancer drugs in the blood stream that attack healthy cells.

A second feature of the plant virus is that its automatic release of cargo is not instantaneous once the virus enters a cell. This allows time for the licensed two-stage targeting in which nuclear importins attached to the nanoparticle guide it into the cell nucleus, where it unloads its therapeutic agent, thereby maximizing efficacy and evading the cancer cell defenses. Delivery to the nucleus overcomes multi-drug resistance that occurs with current drug therapies.

Robustly protecting its cargo in very harsh environments is another property of the NanoVector plant virus nanoparticle. Unlike other viruses, the NanoVector plant virus is non-toxic to humans and, without specific cell targeting, will not accumulate in any body organs or otherwise healthy tissue. This makes it the perfect vehicle for targeted intracellular therapeutics.

NOVEMBER 2008

TheraQuest's IND for Abuse Deterrent Strong Opioid (TQ-1015) Accepted by FDA

NewsRx.com: November 30, 2008 – TheraQuest Biosciences, Inc., a development-stage pain management company, has announced that the U.S. Food and Drug Administration (FDA) has accepted its Investigational New Drug (IND) application for TQ-1015, its abuse deterrent, extended-release strong opioid. TQ-1015 is being developed using SECUREL®, TheraQuest's proprietary abuse deterrent technology.

Najib Babul, Pharm.D., chief executive officer of TheraQuest, stated, "Sustained release opioids are the standard of care for the management of chronic pain. Unfortunately, it is easy to defeat the sustained release mechanism of such dosage forms, making them subject to drug diversion and drug abuse. The TQ-1015 dosage form is highly tamper resistant, when compared to OxyContin®, thereby minimizing abuse by recreational drug users and drug addicts."

BioMimetic Therapeutics Reports Patent Allowance from U.S. Patent and Trademark Office for PDGF Compositions Patent

November 29, 2008 – BioMimetic Therapeutics, Inc. has announced that the U.S. Patent Office has allowed the company's U.S. patent application (No. 11/159,533) titled "Platelet-Derived Growth Factor Compositions and Methods of Use Thereof."

The allowed claims within this patent application cover compositions of platelet-derived growth factor (PDGF)

combined with matrix materials having defined characteristics, which cover the company's novel recombinant protein-device combination product candidates, including Augment Bone Graft and Augment Injectable Bone Graft. The new patent will remain in force until 2024, during which time it will prohibit the marketing of similar or generic versions of Augment, Augment Injectable, GEM 21S, and potentially other products the company has in development.

"We are tremendously excited by the allowance of this patent. I believe it is one of the Company's most important accomplishments since our Initial Public Offering," said Dr. Samuel Lynch, president and CEO of BioMimetic Therapeutics, and the inventor named on the patent. "It is a major step in building our patent portfolio and will enable us to exclude potential competitors from marketing PDGF containing products similar to ours containing critical formulations and dosages of PDGF until at least 2024. Allowance of this patent significantly extends the Company's exclusivity period during which we can realize the full economic benefits of our proprietary PDGF technology platform."

CPEX Pharmaceuticals Announces Publication in *Journal of Diabetes Science and Technology*

NewsRx.com: November 24, 2008 – CPEX Pharmaceuticals, Inc. (NASDAQ: CPEX) has announced the publication of study results of a clinical trial with the company's proprietary investigational intranasal insulin candidate, Nasulin™, in the November 2008 issue of the *Journal of Diabetes Science and Technology*. In a peer-reviewed article titled "Pharmacokinetics and Pharmacodynamics of Intranasal Insulin Spray (Nasulin™) Administered to Healthy Male Volunteers: Influence of the Nasal Cycle," the authors reported that the intranasal insulin formulation was generally well tolerated and well absorbed and that the drug can be administered without regard to the nasal cycle. The study was conducted by investigators from the National University of Ireland, Cork & Shandon Clinic, and CPEX Pharmaceuticals.

"We believe this publication provides meaningful information as CPEX continues development of further clinical studies for Nasulin and helps expand knowledge and interest among healthcare professionals treating diabetes," stated John Sedor, president and CEO of CPEX Pharmaceuticals. "The data from the study are encouraging and support the importance of a differentiated treatment option like Nasulin™ for diabetic patients." The full article is available on the *Journal of Diabetes Science and Technology* website (www.journalofdst.org).

Emisphere Announces Study Results of New, Orally Bioavailable Formulation of Parathyroid Hormone (PTH) Using Eligen® Technology

Globe Newswire: November 24, 2008 – CEDAR KNOLLS, N.J. – Emisphere Technologies, Inc. (Nasdaq: EMIS) has announced the results of a study by Novartis Pharma AG that demonstrates the achievement of a suitable PK profile of a new oral formulation of parathyroid hormone (PTH) using Emisphere's Eligen® technology. This initial study of 20 healthy

postmenopausal female patients aged 40–70 years resulted in peak concentrations (C_{MAX}) in the range of those obtained with the commercially available subcutaneous formulation Forteo (teriparatide). The plan is to continue the development program.

Recombinant PTH, currently approved for the treatment of osteoporosis, is available only by injection. PTH exists naturally in the body; it increases bone density and bone strength to help prevent fractures. It may also be used to treat osteoporosis in patients at high risk of bone fracture.

“As with the development of any drug, these study results were very critical. They may confirm the formulation and the technology and set the stage for an important development plan which will now follow,” said Michael V. Novinski, president and chief executive officer of Emisphere Technologies, Inc. “Oral PTH is a significant early-stage product to the Emisphere pipeline, albeit earlier stage.” This initial trial reported no significant adverse effects, no hypocalcaemia, and no drug-exposure related discontinuation.

Lipocine Establishes Clinical Feasibility of Once-a-Day Ziprasidone

November 24, 2008 – Lipocine Inc. (www.lipocine.com), a specialty pharmaceutical company that uses clinically validated proprietary technologies to address key unmet drug delivery and therapeutic needs, has successfully completed a clinical study that establishes the feasibility of the first once-a-day dosing product for Ziprasidone, a leading treatment for schizophrenia and bipolar disorder.

Commenting on this development, President and CEO Mahesh Patel said, “Our patented Lip’ral®-SSR technology enabled this breakthrough for the ‘once-a-day’ formulation that will improve patient compliance in a meaningful way for schizophrenia and bipolar disorder sufferers. In addition, sustained release formulations enabled by Lipocine’s Lip’ral®-SSR technology offers the potential to improve therapy and side effect profile for drugs such as Ziprasidone.”

Lip’ral® and Lip’ral®-SSR are clinically proven oral delivery technologies for water-insoluble drugs that improve absorption and can be extended to enable controlled release of insoluble drugs and drugs with pH-sensitive solubility. Multiple patents have been issued and are pending on these proprietary technologies.

Solvay Pharmaceuticals, Inc. Announces Exclusive North American License Agreement with Depomed, Inc. for Gabapentin GR® for the Treatment of Neuropathic Pain

Business Wire: November 20, 2008 – MARIETTA, Ga. – Solvay Pharmaceuticals, Inc. has announced a product license agreement with Depomed, Inc. (NASDAQ: DEPO) under which Solvay Pharmaceuticals will have exclusive rights for Gabapentin GR® (also referred as DM-1796) for the treatment of neuropathic pain in the United States, Canada, Mexico, and Puerto Rico.

Gabapentin GR® is an investigational gastric retentive formulation of gabapentin that is designed to reduce the dosing frequency and aims at reducing some of the side effects associated with gabapentin. Currently in Phase III development, Gabapentin GR® is administered once daily and is being studied for the treatment of postherpetic neuralgia (PHN).

MicroCHIPS Awarded AAPS 2008 Drug Delivery Technology Award

PRNewswire: November 17, 2008 – BEDFORD, Mass. – MicroCHIPS, a developer of intelligent implanted devices, has been selected as the inaugural recipient of the 2008 AAPS Drug Delivery Technology Award at the Annual Meeting of the American Association of Pharmaceutical Scientists in Atlanta. The new award recognizes outstanding research pertaining to novel drug delivery technologies.

John Santini, Jr., Ph.D., president and CEO of MicroCHIPS, will accept the award and present an overview of MicroCHIPS’s innovative technology in a talk titled, “Achieving Protein and Peptide Delivery Through Novel Microreservoir Platforms.” MicroCHIPS is developing next-generation drug delivery and biosensing devices to increase therapeutic control and effectiveness for people with diabetes, osteoporosis, and other debilitating diseases.

“Many potent therapeutics aren’t effective because of hurdles associated with drug delivery,” said Dr. Santini. “Microreservoirs, integrated in long-term implants with wireless communications, can address issues of patient compliance, long-term drug stability, and the need for precisely-timed delivery. We are honored that our work has been recognized for its potential to help millions of people with chronic conditions.” “This prize is a tribute to the leading research being done by the team at MicroCHIPS,” said Robert Langer, Sc.D., Institute Professor at the Massachusetts Institute of Technology and a MicroCHIPS co-founder. “The technology they are developing has important applications in clinical areas with significant unmet needs, both for drug delivery and for biosensing.”

MicroCHIPS’s award-winning research in drug delivery is focused on the development of a long-term implant for osteoporosis therapy. The microreservoir-based device is being developed to conveniently deliver hPTH(1-34) to help build bone, prevent new fractures, and improve quality of life for those who suffer from osteoporosis. Affecting an estimated 75 million people in Europe, the United States, and Japan, osteoporosis can lead to debilitating fractures and significant morbidity, especially in elderly patients.

US FDA Approves 30-Minute Onset of Action for Focalin® XR, Bringing Potential Benefits to ADHD Patients During Early Morning Period

PRNewswire: November 12, 2008 – EAST HANOVER, N.J. – The U.S. Food and Drug Administration (FDA) has approved a 30-minute onset of action for Focalin® XR (dexamethyl-

In the News continued from page 51

phenidate HCl) extended-release capsules for the treatment of attention deficit/hyperactivity disorder (ADHD), bringing potential benefits for young patients and their families during the important morning period when they are preparing for school.

“The morning is a critical time for families,” said Alice Mao, MD, associate professor of psychiatry at the Baylor College of Medicine. “The early onset of Focalin XR provides symptom control which may help families and children living with ADHD get through their morning routine.” The new labeling is based on clinical study data. The most recent study, involving 86 children with ADHD between the ages of 6 and 12, showed that Focalin® XR provided significant improvements at 30 minutes post-dose compared with placebo in measures of attention, deportment, and academic productivity.

“The 30-minute onset of action can help children with ADHD improve their morning academic productivity in school. Focalin XR also allows them to effectively manage their symptoms for up to 12 hours getting them through school and homework time,” said Rafael Muniz, MD, senior medical director, Novartis Pharmaceuticals Corporation.

Research Reported by Scientists at Jadavpur University, Department of Pharmaceutical Technology

NewsRx.com: November 7, 2008 – Research is reported in detail in “Extended Release Dosage Form of Glipizide: Development and Validation of a Level A *In Vitro-In Vivo* Correlation.”

According to a study from India, “Defining a quantitative and reliable relationship between *in vitro* drug release and *in vivo* absorption is highly desired for rational development, optimization, and evaluation of controlled-release dosage forms and manufacturing process. During the development of [a] once daily extended-release (ER) tablet of glipizide, a predictive *in vitro* drug release method was designed and statistically evaluated using three formulations with varying release rates.”

“In order to establish internally and externally validated level A *in vitro-in vivo* correlation (IVIVC), a total of three different ER formulations of glipizide were used to evaluate a linear IVIVC model based on the *in vitro* test method. For internal validation, a single-dose four-way cross over study (n=6) was performed using fast-, moderate-, and slow-releasing ER formulations and an immediate-release (IR) of glipizide as reference. *In vitro* release rate data were obtained for each formulation using the United States Pharmacopeia (USP) apparatus II, paddle stirrer at 50 and 100 rev. min⁻¹ in 0.1 M hydrochloric acid (HCl) and pH 6.8 phosphate buffer. The *f*² metric (similarity factor) was used to analyze the dissolution data. The formulations were compared using area under the plasma concentration-time curve, AUC_{0-infinity}, time to reach peak plasma concentration, T_{max}, and peak plasma concentration, C_{max}, while correlation was determined between *in vitro* release and *in vivo* absorption. A linear correlation model was developed using percent absorbed data versus percent dissolved from the three

formulations. Predicted glipizide concentrations were obtained by convolution of the *in vivo* absorption rates. Prediction errors were estimated for C_{max} and AUC_{0-infinity} to determine the validity of the correlation. Apparatus II, pH 6.8 at 100 rev. min⁻¹ was found to be the most discriminating dissolution method,” wrote A. Ghosh and colleagues, Jadavpur University, Department of Pharmaceutical Technology.

The researchers concluded, “Linear regression analysis of the mean percentage of dose absorbed versus the mean percentage of *in vitro* release resulted in a significant correlation (*r*² ≥ 0.9) for the three formulations.” Ghosh and colleagues published their study in the *Biological and Pharmaceutical Bulletin* (Biological and Pharmaceutical Bulletin, 2008;31(10):1946-51).

OCTOBER 2008

Elixir Medical Corporation Licenses Myolimus from Novartis Pharma AG for Site-Specific Drug Delivery Applications

NewsRx.com: October 31, 2008 – Elixir Medical Corporation has entered into a co-exclusive worldwide license agreement with Novartis Pharma AG granting Elixir the rights to utilize the drug Myolimus with Elixir’s vascular and other site-specific drug-delivery applications. In addition, Elixir has an exclusive worldwide license for use of Myolimus in fully biodegradable stents. “Elixir is committed to be a leader in the drug eluting stent market through the efficient development of a broad and innovative portfolio of DES products to better address physician and patient needs,” said Motasim Sirhan, chief executive officer of Elixir Medical Corporation. “The license agreement with Novartis Pharma AG for Myolimus enhances our capabilities to develop innovative product platforms for our physicians and patients.”

Myolimus, a macrocyclic lactone in the same family as Rapamycin, has demonstrated impressive versatility, stability, and a broad therapeutic index. The macrocyclic lactone drugs represent the most widely utilized drug family for drug-eluting stent applications and have an established safety and efficacy profile. Elixir observed positive results from evaluating the safety and effectiveness of Myolimus for the prevention of restenosis through extensive pre-clinical testing, including *in vivo* animal studies and *in vitro* testing conducted over the past several years.

Elixir continues to make excellent progress with its proprietary macrocyclic lactone drug Novolimus. Twelve-month follow up from the Excella I first-in-man study has been successfully completed and will be presented at the upcoming TCT DES Summit. The company initiated the Excella II multi-center randomized clinical trial in the fourth quarter of 2008. Data from Excella II will be submitted for CE mark approval of the Novolimus eluting coronary stent system.

Agile Therapeutics Announces Issuance of Key Patents for Its SKINFUSION™ Technology in Contraception

Market Wire: October 28, 2008 – PRINCETON, N.J. – Agile Therapeutics, Inc., a late-stage pharmaceutical company specializing in women’s health products, has announced that the U.S. Patent and Trademark Office (USPTO) has issued two patents for its proprietary transdermal delivery technology. The patents (US 7,045,145 and US 7,384,650) for the company’s SKINFUSION™ technology covers the intermediate formulation during manufacturing and the finished product for a transdermal patch containing estrogen and progestin used in contraception. Agile’s lead product, AG200-15, is a new, innovative, low-dose, weekly contraceptive patch entering Phase III clinical development. The patch will provide women with a convenient alternative to oral contraceptives by avoiding the need to remember to take a pill every day.

The patents represent a key advancement in the development of transdermal delivery systems. SKINFUSION™ technology utilizes passive enhancement chemistry (PEC) in a dual delivery system consisting of an active and peripheral adhesive system that delivers hormones at levels necessary to prevent pregnancy. The company has filed an additional patent application covering the active adhesive system, which utilizes a unique combination of enhancers to provide balanced delivery of drug over 7 days. In addition, patent applications have been filed to protect intellectual property rights in the peripheral adhesive system, which maintains drug stability while improving patch adhesion and comfort.

Thomas Rossi, Ph.D., president and chief executive officer of Agile Therapeutics, Inc., said, “SKINFUSION™ technology is a significant advancement in contraception, providing women with the trusted hormonal combination of levonorgestrel and ethinyl estradiol in a low-dose, weekly contraceptive patch that is comfortable to wear. We expect our patents to protect this important asset for Agile well into the future.”

NanoBio Demonstrates New Topical Approach to Treating Nail Fungus that Circumvents Problems with Current Therapy

PRNewswire: October 27, 2008 – WASHINGTON, D.C. – A novel topical therapy for nail fungus, NB-002, has demonstrated a new topical approach to healing nail fungus by penetrating skin pores and diffusing through the skin that surrounds the entire nail plate, according to a study conducted by NanoBio Corporation. The data represent a unique approach to treating nail fungus (onychomycosis), which resists topical therapies because they cannot penetrate the nail and access the site of infection. The results were reported at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/Infectious Diseases Society of

America (IDSA) 46th Annual Meeting in Washington, DC. “In testing NB-002 on human cadaver skin, we have demonstrated that the lotion permeates and then laterally diffuses across tissue plains in the epidermis and the dermis to more than 1 centimeter away from the site of application,” said Susan Ciotti, Ph.D., director of formulations and research and development, and presenting author of the data. “The average great toenail measures 22 millimeters across, so we are able to deliver NB-002 across the entire span of an infected human large toenail, a huge advance in the treatment of onychomycosis,” Ciotti said.

Because of its novel mode of penetration and diffusion, NB-002 is able to achieve 50 times the minimum drug concentration required to kill the fungus in the very center of the nail bed. Only 4 µg/g of tissue is required for NB-002 to kill fungal infections.

NanoBio scientists credit the topical lotion’s safety and robust anti-infective activity to NB-002’s novel technology platform. The lotion is composed of an oil-in-water emulsion and a commonly used antimicrobial surfactant that are mixed at high speeds to nanosize the particles and infuse them with high levels of potential energy. The resulting nanodroplets easily penetrate hair follicles and skin pores to reach the site of infection without damaging or irritating skin or mucous membranes. Upon contact with the pathogen, the highly charged particles release their energy to the pathogen’s outer membranes, disrupting the fungus. NB-002 is currently being studied in a randomized, double-blind, placebo-controlled, Phase II trial in more than 400 subjects with onychomycosis. Final results are expected in the first quarter of 2009.

Oxygen Biotherapeutics, Inc. Reports on FDA Meeting, Next Oxycyte® Clinical Trial, and Development Direction

Business Wire: October 23, 2008 – COSTA MESA, Calif. – Oxygen Biotherapeutics, Inc. (OTCBB: OXBO) has announced that it had a very fruitful and productive scientific meeting with the FDA to discuss the safety and development of Oxycyte® in traumatic brain injury (TBI). Oxycyte is the company’s perfluorocarbon (PFC) therapeutic oxygen carrier.

The company has subsequently decided to expand its research plan to include a sequential dose-escalation safety and efficacy study of up to 40 patients. Due to the slight redesign of the protocol and administrative processes, patient enrollment is anticipated to begin in the first quarter of 2009. The company intends to conduct the study in the United States, with a second study planned in Canada. A possible additional study in Switzerland is under review, and a decision on that will be made in the near future. ■

2009

AAPS Workshop on Scientific and Technological Advances in the Use of Lipid-based Drug Delivery Systems for Bioavailability Enhancement and Tissue Targeting

Co-Sponsored with CRS, AIChe, SBE, EUFEPS, and ISPE

March 10-11

Sheraton Inner Harbor Hotel
Baltimore, Maryland, U.S.A.

www.controlledreleasesociety.org/main/meetings/

CRS German Chapter Annual Meeting and Young Scientist Meeting in Pharmaceuticals

March 19-20

Martin Luther University of Halle-Wittenberg
Halle, Germany

www.controlledreleasesociety.org/main/meetings/

Oral Multi-Particulate Drug Delivery Systems: Challenges and Opportunities

March 24-25

Hilton Vienna Danube
Vienna, Austria

www.controlledreleasesociety.org/main/meetings

ISOPS 9th International Symposium on Pharmaceutical Sciences

June 23-26

Ankara University, Faculty of Pharmacy
Ankara, Turkey

www.pharmacy.ankara.edu.tr

36th Annual Meeting & Exposition of the Controlled Release Society

July 18-22

Bella Center
Copenhagen, Denmark

www.controlledreleasesociety.org/main/meetings

2010

37th Annual Meeting & Exposition of the Controlled Release Society

July 10-14

Oregon Convention Center
Portland, Oregon, U.S.A.

www.controlledreleasesociety.org/main/meetings

2011

38th Annual Meeting & Exposition of the Controlled Release Society

July 30-August 3

Gaylord National Resort and Convention Center

National Harbor, Maryland, U.S.A.

www.controlledreleasesociety.org/main/meetings



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

NON-PROFIT ORG.
U.S. POSTAGE
PAID
MINNEAPOLIS, MN
PERMIT NO. 4656