CONTROLLED RELEASE SOCIETY
Volume 19 • Number 3 • 2002

NEWSLETTER

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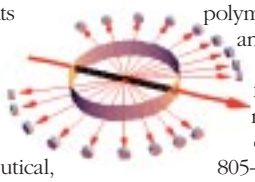

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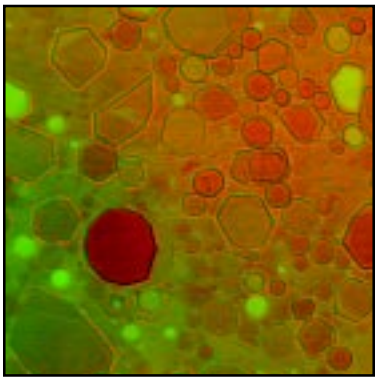

Polyhedral drug delivery vesicles. Photo provided by Doctors, I. F. Uchegbu, A.G. Schatzlein, and A.T. Florence, School of Pharmacy, University of London.

Dedicated to the science and technology of controlled release and delivery and promoting education by releasing science to deliver a better future.

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

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From the Editor

By Bo Michniak

It was with sadness that I learned that my colleague David Friend had decided to resign from his position as Co-Editor of the Newsletter. Dave had been Editor for many years and invited me to help him with this task about a year ago. I think you will all agree that he did a wonderful job during his tenure. We wish him well in all his future ventures. Meanwhile, I would like to welcome our new Co-Editor on board, Ijeoma Uchegbu Ph.D. and Consumer & Diversified Products Special Feature Editor, Jerome Barra Ph.D.

Dr. Uchegbu

Dr. Uchegbu is currently a Senior Lecturer in drug delivery at the University of Strathclyde in Glasgow, U.K. She graduated with a degree in pharmacy from the University of Benin in Nigeria, obtained a Masters degree from the University of Lagos (also in Nigeria) and studied for a Ph.D. degree in drug delivery at the University of London School of Pharmacy, graduating in 1994. After a postdoctoral fellowship at the same institution, she was appointed to a lectureship at the University of Strathclyde in 1997. Her research is focused on the design, synthesis and characterization of amphiphilic polymers. Such polymers and small molecular weight amphiphilies have been used to prepare vesicles, micellar systems and gels to facilitate drug/gene delivery and targeting.

Dr. Barra

Dr. Barra graduated as a Pharm.D. from University of Paris-Sud in France and then obtained a Masters Degree in Biopharmacy and Pharmaceutical Technology from the same University, focusing on the physics of compression. Dr. Barra then joined the French National Institute of Scientific Medical Research working on AIDS-related clinical trials. The Laboratoires UPSA (now a French sub-division of BMS) offered him a Ph.D. sponsorship in collaboration with the Department of Pharmaceutical Technology and Biopharmacy of the University of Geneva (Switzerland) where he also became an Assistant of Dr. E. Doelker. After 4 years working on the potentials of solubility parameter and surface energy in pharmaceutical formulation, Dr. Barra joined Firmenich SA, a world leading flavor and fragrance house, in Geneva (Switzerland) in 1999 as Pharmaceutical Technology Manager where he created a dedicated pharmaceutical development laboratory for flavoring active ingredients. Some areas of investigation, in collaboration with internal research fellows, include flavor interactions with active ingredients or packaging, bitter masking, flavor perception, and performance of flavor delivery systems in pharmaceutical and non-pharmaceutical applications.

We now have one U.S. based Editor and one in Europe which allows the newsletter to be even more global. We hope to expand the Newsletter by adding more features such as interviews with top scientists in the areas of controlled release and updates on novel technologies. We are looking for volunteers to contribute articles or features in many areas, including: gene delivery, diagnostics, tissue engineering, veterinary/agriculture, injectable microcapsules, peptide and protein delivery; the list goes on. Please feel free to contact the Editors, we welcome ideas and comments about the Newsletter. Email newsletter@controlledrelease.org

Call For Nominations

Wanted: Nominations for Board and Scientific Advisors.

The Nominating Committee is seeking candidates for the Board of Directors and the Board of Scientific Advisors. Nominations are being sought for the following positions:

Board of Scientific Advisors – 5 Board Members
Board of Directors – Vice President, Member-at-large

The Committee will consider all nominations. Nominations by petition must be signed by at least 30 members of the Society and submitted to the Scientific Secretary, Martyn Davies at Nominations@controlledrelease.org by January 1st of the election year (2003).

Passing the Gavel

By Rosealee M. Lee

Many thanks to Kinam Park who served as President of CRS during the 2001-2002 governance year. Dr. Park brought wisdom and leadership skills to the position, and was an integral part of CRS activities during the past year. The President of CRS devotes many hours each week to the Society, and we appreciate the energy that Dr. Park gave to CRS. When last seen, he was on a golf course, enjoying his new found "leisure" time.

Each year during the CRS Annual Meeting, the gavel is passed from outgoing to incoming President. The gavel itself is, of course, ceremonial. More relevant is the governance of the Society, the vision of the members, Board of Directors and previous Presidents that is also passed.

Kinam Park presents Ceremonial gavel to President Florence

Alexander (Sandy) Florence assumed the Presidency on July 23, 2003. Dr. Florence brings numerous skills as a statesman and consensus-builder to the position, and members who were in attendance as the gavel was passed will affirm he is also a brilliant orator.

Dr. Florence is Dean of the School of Pharmacy, University of London, a role he has always combined with directing a research group. He is editor-in-chief of the *International Journal of Pharmaceutics* and was founding co-editor, with Dr. Vince Lee, of *The Journal of Drug Targeting*. He is both editor and author of books, and more than two hundred fifty papers, reviews, and book chapters. His research spans a wide variety of controlled release and delivery interests (for example, oral uptake and fate of nanoparticles, novel dendrimers and vesicular systems based on nonionic surfactants) and has earned many awards.

While complete information about Dr. Florence's career is available on his curriculum vitae, we asked about his avocations. After speaking lovingly about his wife, Florence (yes, her real name) and his three grown children, he shared his love for music. Dr. Florence plays the organ every day. Before his scientific and educational duties grew too much, he enjoyed playing the organ in church. His playing is now confined to home and his wife, Florence, is the sole audience and critic. Dr. Florence is also a painter and poet, although his professional responsibilities do not allow much time for them. The pen and easel have been set aside for now, for what Dr. Florence calls his primary passion – work. "I feel very much, when I'm working hard, as we all have to, that the work has merit in itself and one should be dedicated to it. My father was a pharmacist, and he was also very passionate about his work. "

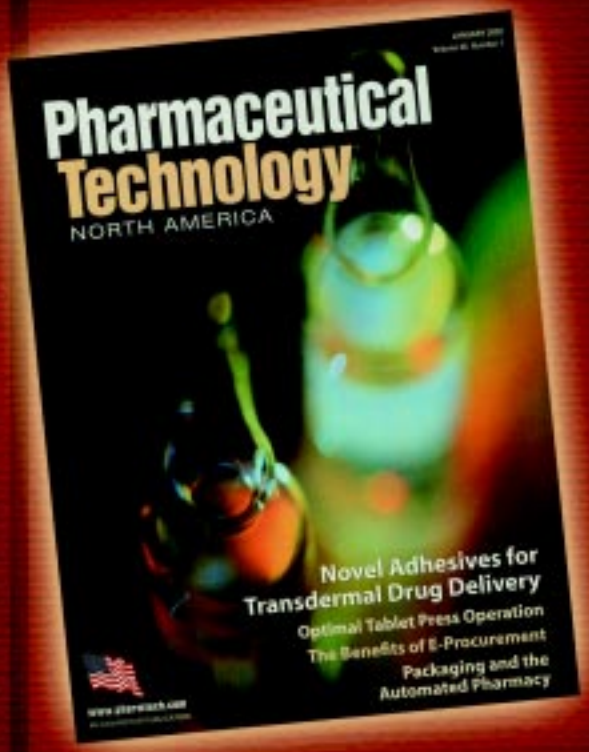
I had the opportunity to visit with Dr. Florence on the first day of his Presidency. When asked how his first day on the job felt, he replied, "A lot of distinguished people have been in this position and one hopes one can add just a little dimension to it – maybe a slightly different perspective."

Dr. Florence expanded upon the message he had presented at the Annual Membership Meeting a few days before. "I think we should try to be more inclusive, particularly of minority interest groups, and not have the whole agenda dictated by those interested in the human medical side. I believe the diversified products area is vital. We need to get people who wouldn't normally come to our meetings like physicists, electronic engineers, pure material scientists, individuals who have another base, so the Controlled Release Society can extend to all branches of the sciences that can improve the science and technology of controlled release. I look to including younger scientists, enthusing and exciting them." He also added, "it's very difficult to bridge between university, industrial laboratories, colleges, and schools. Throughout the world I think people are worried about school children choosing not to go into science, because science is seen to be some sort of dreadful thing that's adversely effected the environment. They don't connect always with new drugs, health care, consumer, agricultural and environmental applications." CRS has a role in interesting the young and uncommitted in the subject.

We spoke about the special role that CRS has as the buttress in healthcare and delivery of medicines for humans and animals, and new and improved consumer and diversified products to help us feel better and live more comfortably. However, if you tell the general public that you are a scientist working in controlled release, their response is a blank stare. Dr. Florence says, "Societies like ours have always been interested in what scientists are working on and publishing it for our members to read. The most difficult thing to do is communicating what we do to a lay audience and getting our message across. Ultimately it is the public that pays our salaries, and we've got to do more to inform the public - and politicians - of what we do. In CRS we need to put our often fascinating and intriguing stories across in a responsible way. That is, not talk about breakthroughs, but the exciting possibilities, and the difficulties of getting there. We need their encouragement and support. The public needs to hear about applications and endpoints, such as 'I try to target drugs to the different parts of the body'. They don't want to hear about specifics."

The next year will be one of dynamic growth and outreach under the direction of President Florence. His agenda to enlarge CRS membership, enhance educational programs, and bring the message of controlled release science to the public, is an extension of the statement he made prior to election, "…this area of science is not accorded the status that it deserves by those that fund research. Fundamental studies in controlled delivery involve exacting science with endpoints that are often more rigorous than those displayed in pure science. The benefit to mankind is obvious. So there is a role for the CRS not only in continuing to organize conferences of high standard and interest but also to engage in a political debate about the vital need for investment in this area of endeavor." We welcome Dr. Florence's vision and energy on behalf of the entire controlled release and delivery community.

Editors Note: Dr. Florence encourages all CRS members to contact him directly regarding any issue. He may be reached by email at president@controlledrelease.org. •



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Talking with the Animals

By Keith J. Ellis
Pharmacology and Bioactive Delivery, CSIRO Livestock Industries, Armidale, NSW Australia

At the Vet-Get-Together of the 2002 Controlled Release Society Annual Symposium (Seoul), a group of animal-oriented members of the Society, together with some whose work has to date been solely human oriented, met to discuss the topic "Human and Veterinary Interactions – what we might learn from each other."

While the subject may appear unusual for a meeting of scientists, the venue was even more so! By courtesy of InterAg NZ , the group assembled, ate and drank (fed and watered?) at the Pul Hyang Gi restaurant in a back street of Seoul City, not far from the conference venue. Being a cultural event, all shoes were removed before entering the dining area, and there were interludes of Korean traditional music and dance throughout the evening. The food was delightful even though a few dishes were of unknown origin ……..however, the traditionally dressed waitresses were ready and willing to help any of the group who had trouble preparing a desired combination of culinary treats. This was the case for one particular ex-President of the Society who demonstrated inadequacies in this endeavour, but in the final count probably had more to eat than most members of the group.

Michael Rathbone, Chairman of the CRS Membership & Development Veterinary Products Subcommittee and InterAg representative, ensured the evening started well by ordering Sujo for all (at 22% alcohol content, it had the desired effect!) to aid the digestion, and during the evening the group was led in the discussion topic by Keith Ellis from CSIRO Australia, who provided interesting distinctions between classes of animals, the ways in which they were treated, and the differences between issues such as cost, efficacy, residues, etc.

Matters raised by the group during discussion varied from the importance of maintaining health and welfare of native animals by pharmacological means in South Africa as an adjunct to both wildlife conservation and the tourism industry, to whether or not there was any value in using animals studies as a prelude to human trials.

All in all, a great night was had by all ….. the interactions between "humans" and "animals" undoubtedly increased as a result, and bears well for next year's conference where it is hoped that Veterinary Products and animal-related issues will receive increased exposure.

The Animal Health Consortium

Michael J. Rathbone, InterAg, Hamilton, NZ
Marilyn N. Martinez, Center for Veterinary Medicine, Food and Drug Administration, Rockville, Maryland, USA

This article discusses the Animal Health Consortium, a recent initiative of the Controlled Release Society Membership & Development Veterinary Products Subcommittee that aims to connect animal health professionals throughout the world.

The animal health community represents a widely diverse group of professionals, dealing with basic science, technology, economics, and issues concerned with animal and public health. Despite this diversity, today's rapidly changing environment necessitates the integration of these multifaceted activities to help each deal with different aspects of the same challenges. While the professional organizations to which each community belongs help to keep them informed of the advances that are occurring within their own unique areas of specialization, current issues arising in veterinary medicine, husbandry practices, drug development, drug regulation, and international marketing and trade necessitate improved intercommunication. Unfortunately, it is often difficult to keep abreast of advances within each individual field, let alone those associated with other disciplines of animal health. For this reason, the Controlled Release Society Membership & Development Veterinary Products Subcommittee created the Animal Health Consortium (AHC), a network of professional organizations intended to help overcome many of the obstacles currently impeding effective inter-discipline communication.

The mission of the AHC is to provide a forum for communication between member organizations via electronic newsletters and web-based interactions.

The AHC website is sponsored by the Controlled Release Society and was developed in order to serve the needs of each individual animal health community. Once every six (6) months, an internet address is sent to over 30 participating organizations through the world that links directly to the most current newsletter. The objective of the biannual newsletter is to distribute important alerts to the international animal health community and to provide updates on upcoming issues or events associated with the various member organizations. The newsletter also provides an opportunity for questions and answers on topics of interest, or simply the sharing of a commentary on animal health issues. The website itself will provide additional features such as requests for collaboration and the posting of résumé's. Please visit our website (http://www.controlledrelease.org/ahc) for more details.

An added feature of the AHC is an email discussion group. As questions and responses are submitted to this discussion group, they will be distributed through a separate AHC discussion group email list. This list will consist of the addresses of individuals who have indicated an interest in being included on the list of email recipients. The organizers believe that learning about the questions, challenges and perspectives of experts from the various aspects of animal health provides an important avenue for widening our own perspectives and enhancing the development of creative solutions to problems we must all address.

It is our hope that this site will continue to evolve as we strive to meet the diverse needs of the Consortium members.

To join the listserve, or to learn more about the AHC, simply follow the instructions on the website (http://www.controlledrelease.org/ahc), or contact Marilyn N. Martinez (within the US on mmartin1@cvm.fda.gov) or Michael J. Rathbone (outside the US on mjr@interag1.co.nz) directly.

Awarding Excellence

The Controlled Release Society was proud to award excellence at the 29th Annual Meeting in Seoul, Korea. The impressive list of winners may be found below. Congratulations to all the distinguished winners and good luck to everyone in Glasgow, Scotland, 2003. Be sure to check the upcoming issues of the CRS Newsletter for more details.

Founders Award
Thomas Kissel from the University of Marburg, was presented the 2002 Founders Award, the Society's most prestigious award, for his outstanding contributions in the science and technology of controlled release. Thomas Kissel was presented a crystal award, $10,000 and grant-in-aid to attend the Seoul, Korea meeting. The award was sponsored by CRS and **ALZA**.

CRS-Nagai Innovation Award
Robert Langer from the Massachusetts Institute of Technology, U.S.A., was awarded the 2002 CRS-Nagai Innovation Award for his exceptional contribution to a successful and innovative controlled release product or technology. Nicholas Peppas accepted the silver-struck medal award and $3,000 for Robert Langer who was not able to be present to accept his award.

Young Investigator
Steven Schwendeman from the University of Michigan, U.S.A., was awarded the 2002 Young Investigator Award for his outstanding research contributions for a younger member of the Society. Steven Schwendeman was presented a silver-struck medal, $1,000 and grant-in-aid to attend the Seoul, Korea meeting.

Eurand Career Achievement
Nicholas A. Peppas, Showalter Distinguished Professor in the Department of Biomedical Engineering at Purdue University, U.S.A., was the 2002 Eurand Award Career Achievement Winner in Oral Drug Delivery.

Eurand Grand Prize
Wei-Chiang Shen, from the University of Southern California, U.S.A., was awarded the 2002 Eurand Award Grand Prize.

Eurand Second Place
Maria José Alonso, of the University of Santiago de Compostela, Spain, was awarded the 2002 Eurand Award Second Place.

Eurand Honorable Mention
Hans E. Junginger, of Leiden University, The Netherlands, was awarded the 2002 Eurand Award Honorable Mention.

Eurand Honorable Mention
Teruna J. Siahaan, of the University of Kansas, U.S.A., was awarded the 2002 Eurand Award Honorable Mention.

Capsugel
From top to bottom: Thiagarajan Sakthivel, Shin-ichi Fujiwara, Keitaro Kadono, and **Guk Hyun Jo** were winners of the 2002 **CRS-Capsugel Graduate/PostDoc Award** on their research of Innovative Aspects of Gastrointestinal Drug Absorption. **Shin-ichi Fujiwara** from Kyoto University, Japan, was selected as the final winner. He was presented a plaque, $1,000, travel expenses, and grant-in-aid to attend the Seoul, Korea meeting.

Jorge Heller
Alison B. Fleming from Cornell University, U.S.A., was awarded the 2002 Jorge Heller *Journal of Controlled Release* Outstanding Paper Award. Alison Fleming was presented a plaque, $1,000 and grant-in-aid to attend the Seoul, Korea meeting. The award was sponsored by CRS and Elsevier Science, B.V.

Outstanding Paper
Andrea Luck of Aventis Pharma Deutschland, was awarded the 2001 Graduate Student Paper Award. Andrea Luck was presented a plaque and grant-in-aid to attend the Soul, Korea meeting. CRS and 3M Drug Delivery Systems sponsored this year's award.

Outstanding Paper
Duxin Sun from the University of Michigan, U.S.A., was awarded a 2001 Graduate Student Paper Award. Duxin Sun was presented a plaque and grant-in-aid to attend the Seoul, Korea meeting. CRS and Cygnus sponsored this year's award.

Outstanding Paper
John Mikszta of BD Technologies, was awarded the 2001 **Outstanding Pharmaceutical Paper Award.** John Mikszta was presented a plaque and grant-in-aid to attend the Seoul, Korea meeting. CRS and Ethypharm sponsored this year's award.

Outstanding Paper
Darrel J. Kesler from the University of Illinois, U.S.A., was awarded the 2001 **Outstanding Veterinary Paper Award**. Darrel Kesler was presented a plaque and grant-in-aid to attend the Seoul, Korea meeting. CRS and Thorn BioScience sponsored this year's award.

Transition

By Rosealee M. Lee

Aren't we always in transition? In our professions and personal lives, we are continually in transition. I have been honored and blessed to serve as the Executive Director of CRS during the past eighteen months. During that time I met and spoke with hundreds of CRS members. As a group, you were both loyal and honest with me about what members needed, and you provided your ideas for the future of CRS. It is now time for me to step aside and let the next wave of professionals do their job.

From our Association Executive Department a new team has been appointed to serve you. Mark Ricker, who has been working with CRS for several months, now serves as Executive Director, and Ronda Thompson serves as Associate Executive Director. Jaymie Griffin, who has worked with you for the last year and one-half has been promoted to Assistant Executive Director. The areas in which each of them will focus are listed below. You may reach all three of the individuals via email at one address: director@controlledrelease.org. From behind the scenes, I will watch CRS grow, and take part in the nurturing of this Society for the future. I look forward to seeing each of you at the 2003 Glasgow meeting. It is our 30th Annual Meeting, and since my duties will be mainly advisory, I hope for lots of opportunities to visit with old and new friends. See you there!

From left: Mark Ricker, Jaymie Griffin, and Ronda Thompson

Editors Note: Rosealee Lee serves as CEO of the ARDEL group, and Chairman of ConveneMachine™.

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Scientifically Speaking

Formulation of Gene Delivery Vectors Offers an Exciting Opportunity for Interdisciplinary Research

Joachim Kohn
Board of Governors, Professor of Chemistry, New Jersey Center for Biomaterials

Introduction

Delivery of genes to human cells for therapeutic benefit is a concept that holds enormous promise for treating a wide variety of conditions. Prominent examples are Parkinson's disease, hemophilia, chronic metabolic disorders, cardiovascular disease, and various forms of cancer. Furthermore, gene delivery has the potential to augment various tissue engineering applications, e.g., by promoting cell proliferation through enhanced production of growth factors and/or cytokines.

Unfortunately, the field of gene delivery has been a victim of attempts to commercialize the technology before the scientific ground work had been fully established. As a consequence, in a frenzied hype, investors pumped millions of dollars into dozens' of start-up companies attempting to bring gene therapies into the clinic with poorly chosen gene targets and less-than-optimal delivery strategies. The resulting failures to show compelling benefits in many clinical trials have discredited the entire field of gene delivery to the point that many venture capital funds will no longer provide support for the commercial development of gene therapies.

While the early commercial ventures failed, the steady research efforts in many laboratories led to a better fundamental understanding of the mechanisms of gene delivery. The important lessons learned now make it possible to envision the successful development of a wide range of gene therapies in the near future. Most experts tend to agree that, with the important exception of better delivery strategies, many of the initial challenges and weaknesses in the design of gene therapies can now be adequately addressed.

The Need for Non-Viral Vectors for the Delivery of Genetic Material to Cells

Gene therapy encompasses two different therapeutic approaches: Gene delivery and antisense oligonucleotide delivery. Once genes have been successfully delivered into cells' nuclei, in a process called transfection, the therapeutic proteins encoded by the genes are produced. Contrary to the delivery of genes, which are designed to lead to the expression of a desirable protein, a therapeutic effect can also be achieved by the delivery of antisense oligonucleotides, which are designed to inhibit the expression of an aberrant gene via binding to its messenger RNA.

The delivery of antisense oligonucleotides and the delivery of genes pose somewhat different problems. In both cases, it is necessary to use a vector that can deliver the genetic material to selected target cells in a form that facilitates their uptake across cellular barriers. However, antisense oligonucleotides only have to be delivered into the cellular cytoplasm, while the delivery of genes requires the additional and difficult step of transport across the nuclear membrane. Antisense oligonucleotides have the advantage of being relatively small molecules, genes tend to be much larger macromolecules. On the other hand, the number of antisense oligonucleotides that have to be delivered into a cell to exhibit a therapeutic effect is often much larger than the number of individual copies of a DNA-based gene.

An ideal vector must be able to penetrate the cell membrane, be taken up intracellularly, direct the genetic material to its intracellular target, and finally release it. Two approaches have been developed to accomplish this rather complex delivery challenge: the use of modified (replication incompetent) viruses containing the desired genes and the use of non-viral vectors (such as liposomes and various synthetic polymers). Both approaches have distinct advantages and disadvantages. For viral vectors, their superior efficiency in delivering the genetic material to specific cells, must be balanced against serious safety concerns and difficulties in large-scale processing. On the other hand, for non-viral vectors, their reduced safety concerns and ease of production in scaleable technologies must be balanced against their low transfection efficiency.

Given the lack of success of gene therapy clinical trials, which have predominantly employed viral vectors, more serious consideration has been given to non-viral vectors for gene and antisense oligonucleotide delivery. However, progress in overcoming the major deficiency of non-viral vectors – low overall efficiency – has been slow. This is the key point where innovative polymer design strategies can make a major contribution to the field of gene delivery. In fact, the lack of sufficiently effective non-viral vectors is the main reason for the prevalent use of viral vectors in all current clinical trials. Most experts in the field, even those using viral vectors in their own work, indicate that non-viral vectors may represent a safer and more rational approach to the delivery of genetic materials to target cells – if only the efficiency of non-viral vectors could be improved.

Important Topics of Scientific Discussion

The collaborations between material scientists and the biologists or clinicians involved in gene delivery often tend to be one-way streets – the material scientists usually send samples to the gene delivery group for testing with little cross-disciplinary understanding of the biological mechanisms involved in gene delivery. Likewise the clinicians or biologists rarely spend the time to understand the chemical intricacies of the materials they tested. It seems that it should be possible to accelerate progress in this intensely researched area of pharmaceutical development by creating a more intense interdisciplinary dialog - not only between materials and biological scientists, but also between scientists from both academia and industry. This was the goal of a recent workshop organized by the New Jersey Center for Biomaterials (http://www.njbiomaterials.org/genedelivery/2002.htm) which was specifically designed to facilitate interdisciplinary interactions between biologists, clinicians, and material scientists. The workshop took place on May 15-16, 2002 in Somerset, New Jersey. To create an environment conducive for discussion, the group of attendees was intentionally

limited to less than 50. To ensure an appropriate balance between the disciplines, as well as between industrial and academic scientists, participation was by invitation only.

The workshop was structured in five focused modules with the topics building from a current status report through exploration of major technical issues. First, the *Current Status of Gene Delivery* was summarized by Edmund Lattime of the Cancer Institute of New Jersey who spoke on *Practical Experience with Current Vector Systems* and by Diane Burgess of the University of Connecticut who spoke on *Current Status in the Formulation of Gene Delivery Systems*.

The next module posed the question *Viral vs. Non-viral Vectors: Is There Common Ground?* The working hypothesis of this discussion was that if biologists simplify the structural complexity of viral vectors, while materials scientists increase the design sophistication and functionality of non-viral vectors, both approaches might converge in a common optimal design. In this module, Joseph Dougherty of Robert Wood Johnson Medical School spoke on *Lessons Materials Scientists Can Learn from the Biology of Viral Gene Transfection Vectors*. Then, David Schaffer of the University of California, Berkeley answered *What Viruses Can Learn from Synthetic Vectors: Parsing Parameter Space for Optimization*. They attempted to define what are the absolutely necessary attributes and properties of a successful gene delivery vector and to specify where non-viral vectors fall short.

A fundamental design goal of cutting-edge research in non-viral vectors is to ensure appropriate cellular trafficking of the gene vector, including escape of the gene vector from the endosome before the endosome becomes a lysosome. Design strategies that allow non-viral vectors to escape from the endosome were discussed in the third module, which was titled *Cellular Trafficking*. Alan Hoffman of the University of Washington discussed *Design of pH-sensitive Polymer Carriers that Can Enhance Release of DNA and Other Drugs from the Endosome* and David Putnam from TransForm Pharmaceuticals, Inc. spoke on *Structure-Function Relationships for Endosomolytic Materials.*

Module 4 explored the different delivery strategies required by antisense oligonucleotides. Charles Roth of Rutgers reviewed the *Similarities and Differences Between Gene and Antisense Delivery* while Bozena Michniak of New Jersey Medical School contributed her experience in *Formulation of an Antisense Oligonucleotide System for Topical Delivery*. Given the problems encountered in developing antisense-based therapies, the discussion considered ways to improve utility of antisense oligonucleotides. The group then discussed whether the limited successes have been due to a "delivery" problem, or are the failures in the past associated with the approach itself?

In response to the variety of needs stated in the first four modules, Module 5 presented four specific examples of new, non-viral vector designs, from a materials science perspective. Hamid Ghandehari of the University of Maryland spoke on *Genetically Engineered Polymers for Controlled Gene Delivery*. Dan Luo of Cornell University spoke on *Silica, Nanoparticles, PLGA/PLA Microspheres, and PEG conjugated Dendrimers*. Joachim Kohn of Rutgers announced the *Use of Triblock Copolymer Based, Self-assembled Vesicles for Gene Transfection*. Axel Stemberger and Christian Plank of the Technical University of Munich described *New Materials for Non-viral Gene Transfer to Improve Wound Healing, Including the Use of Magnetofection to Improve the Transfection Efficiency*. The full group considered how to apply the lessons learned during the day to guide the further improvement of their non-viral vector systems.

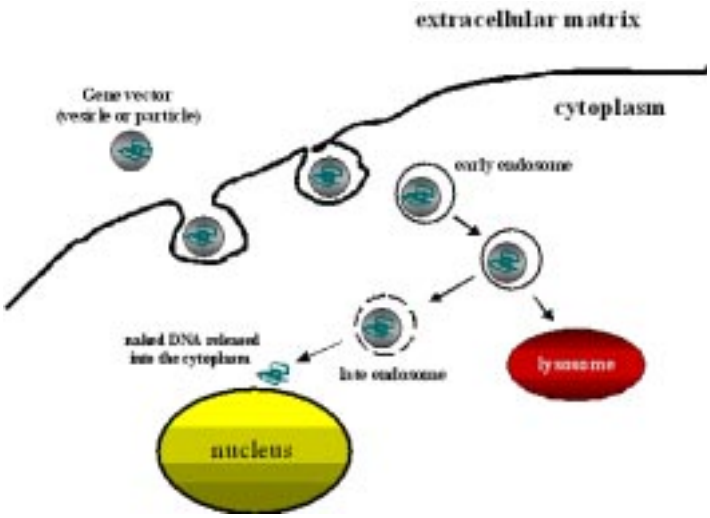

Figure 1: Cellular uptake of a vesicular or particular gene vector (courtesy of Dr. Agnes Seyda, New Jersey Center for Biomaterials). The gene vector is taken up by the cell by a process called "endocytosis". This uptake mechanism results in the incorporation of the gene vector within an endosome. Normally, the endosome becomes a lysosome within a short period of time. Any genetic material within the lysosome is then rapidly degraded. Therefore, successful delivery of the genetic material depends on the ability of the gene vector to escape from the endosome and to release its genetic material into the cytoplasm before the endosome turns into a lysosome.

Conclusions

The workshop illustrated the great need for closer interdisciplinary collaboration and the potential for such endeavors in the field of non-viral vector design. For example, material scientists attempting to design more effective non-viral vectors need to be fully aware of the details of intracellular trafficking. Figure 1 shows in a schematic fashion the steps of cellular uptake and intracellular trafficking of a gene delivery vector. One of the key reasons for the low efficiency of non-viral vectors in delivering genetic material to the cytoplasm, is their inability to release their genetic material from the endosome before the endosome turns into a lysosome. It is estimated that a gene vector has only about 40 minutes from the moment it has been taken up by the cell and incorporated into an endosome, before any residual genetic material is rapidly degraded within the lysosome.

The need for the gene vector to be able to release its payload of genetic material within the endosome poses an extremely difficult challenge to the materials scientist: On the one hand, the gene vector has to be robust, it has to have sufficient stability to keep its genetic material firmly encapsulated during storage, injection into the blood stream, and while outside the target cell. Yet, once inside the target cell, it has to rapidly degrade and/or release the genetic material. Viruses have evolved to address this challenge: Within the endosome, the viral envelope proteins change their conformation, allowing the escape of the virus from the endosome. Obviously, to mimic the biological function of viruses, non-viral vectors have to be designed to respond to environmental stimuli, such as, for example, the lower pH encountered within endosomes. Without this key biological insight, the tendency of most material scientists would be to optimize the binding strength between vector and gene, resulting in a vector that is too stable to be an effective delivery vehicle. •

Patent Watch

Consumer & Diversified Products

By Jack Burger

In the first six months of 2002, a total of 169 new patents were found on the encapsulation of flavours and food additives via the Derwent World Patent Index. In Korea, 7 patents were published. China and Japan filed 12 and 23 new patents, respectively. In the US, 20 patents were published and in Europe 37. The number of WO patents was 70.

EMULSIONS, (SPRAY) DRYING & AGGLOMERATION

Five patents on the use of oil-in-water ***emulsions*** as delivery systems were filed for e.g. tea tree oil useful in medical applications (US 20020001601), for a water-soluble creamer used as a cold beverage creamer for ice slurry beverages (US 20010041211) and as a method to include anti-plaque agents in chewing gum or toothpaste with reduced bitterness and improved sensory acceptability (US 20010047009).

Drying of concentrated aqueous and non-aqueous solutions or emulsions via solvent evaporation under reduced pressure followed by grinding of the resulting product was patented five times. For example, in WO 200208182, a granular water-dispersible powdered carotenoid formulation was made for use as food colorant. The manufacture of crunchy bacon bits from raw bellies via cooking under vacuum is described in US 20020031599.

Spray drying was again the favourite encapsulation technology to obtain powdery delivery systems. In this period, 29 patents were filed in which spray drying was used either to convert liquids into powders or to make delivery systems with well-described characteristics. Examples of making powders via spray drying are described in patents from **Dong Suh Co Ltd** (KR 2001063336 and KR 2001073975) in which a method is described for preparing mixed tea containing a powdered extract of Cascara Sagrada, from **Guangdong Huacheng Food Co** (CN 1318309) with an instant tea powder producing process and from **Nutrasweet Co** (WO 200205660) for the production of a product containing neotame in presence of a co-agent like maltodextrin. **Bestfoods** (EP 1190627) filed a patent on the production of a natural mushroom flavouring after enzyme treatment of the fungal material followed by spray drying. Food products having a caramel flavour obtained by heating and caramelizing saccharides, mixing with dairy products and spray drying of the milky liquid is patented by **Nippon Seinyu KK** (JP 2002034449). **Natural AS** (WO 200178531) claims to have a spray dried powder useful as dietary supplement, having a high amount of conjugated linoleic acid. The powder is free flowing, odourless and has good organoleptic properties. An interesting patent on materials with film forming properties for spray drying was filed by **Australian Food Center** (WO 200174175). An oxygen sensitive oil was encapsulated within a film-forming protein, which prior to drying, was heated in solution in the presence of a carbohydrate to obtain Maillard reaction products providing resistance to oxidation.

Agglomeration (or granulation) is often applied in combination with or following to spray drying. In JP 2002045675, **Ajinomoto KK** is patenting a spray drying granulation device for the preparation of granular form food products comprising a conical housing supplied with air current in downward direction from the upper end. **Ajinomoto** (JP 2001309751) is using granulation to prepare additives for feed from grinded Cassava potato particles of 150 micron, which were dry granulated after saccharification and fermentation. Agglomeration is also used to make particles consisting of starch and maltodextrin which instantly disperse and simultaneously develop full viscosity in a cold water-containing medium like instant bakery products (**Cerestar**, EP 1166645).

COATING PROCESSES

Although not really a coating technology, hard fats are often used to encapsulate actives via melting of the fat, dispersion of the active in the molten fat, cooling and grinding of the hardened mixture. In this way, **Unilever** has encapsulated a flavouring system for baked goods and snacks (EP 1175836, US 6312751) and health components for food products like cheese and ice-cream (EP 1161879). In FR 2811203 from **Microlithe**, microcapsules of coffee were prepared by blending a natural or synthetic coffee flavour with a hydrogenated coffee or vegetable oil, followed by mixing with powdered coffee and grinding. In the same way, **Omegatech** incorporated polyunsaturated fatty acids into a protective fat (WO 200200028).

Fluid bed coating processes were used in a number of patents. For example, in JP 2001269133, **Daitsu KK** have coated wheat flour and other powders with liquid seasonings like vinegar, soy sauce and alcoholic drinks. Coating has also been used in chewing gum. **Wrigley** (US 6322806) filed a patent on a chewing gum for delivering of a medicament comprising a tableted gum center, comprising a water-soluble portion and a water insoluble portion, and a coating comprising a medicament that surrounds the tableted gum center. According to Wrigley, drug absorption into the systemic system will be enhanced. Amongst others, **Wrigley** (WO 200217731) patented a method of making antacid chewing gum (viz. calcium carbonate with a mean particle size of greater than about 3 micron) via applying a coating syrup to the chewing gum core and drying the syrup to produce a sugarless coating onto the cores. An interesting patent on

coating was filed by **Texa** (WO 200196023). They made a dielectrically-engineered microparticle comprising a conductive core and an insulating self-assembled monolayer coating the conductive core, where the monolayer has a thickness sufficient to render the microparticle maneuverable by dielectrophoresis. These particles might be useful for detection purposes in e.g. food, food processing and food distribution.

COACERVATION

In this period, no patents were found on complex coacervation of flavours using the traditional gelatin/gum Arabic mixture. Microcapsule formation following phase separation from alginate or chitosan was patented by **Primacare** (EP 1129771), **Cognis** (EP 1184029) and **Perfetti** (WO 200180661). The Primacare patent describes the formation of 0.1-5 mm particles from an oil-in-water emulsion, which is first mixed with an aqueous solution of an anionic polymer and then added to a chitosan solution, resulting in microcapsule formation. The microcapsules are claimed to be useful in cosmetics, pharmaceutical and food products. The Cognis patent claims chitosan microcapsules with encapsulated actives for oral and dental care products to prevent diseases of the teeth or gums. Perfetti claims in their patent chewing gum compositions containing abrasive filler substances encapsulated in cross-linked alginate microspheres for oral hygiene and removal and prevention of dental plaque formation. The alginate particles may further comprise small amounts of flavourings and colourings.

NEW MATERIALS

In 3 patents (WO 200191721, 200192400 and 200192401), **Staley Mfg** claims gelatin-free film forming compositions for forming flexible films made from starch material and a primary external plasticizer. The starch material, which can be modified starch or waxy starch, has a dextrose equivalent less than 1. The weight ratio of plasticizer to starch is at least 0.5:1. The new material can be used to form capsules with a sealed wall.

MISCELLANEOUS

Two patents were issued by **General Mills** on the encapsulation of active materials in a ***glassy matrix***. In WO 200197637, a mineral/vitamin mixture is encapsulated by mixing the mixture with an edible oil into a slurry. The slurry is mixed with a melt comprising molten glass-forming matrix material to obtain a molten blend. The molten blend is then cooled to encapsulate the oil encapsulated mineral or vitamin in a glassy matrix to be used in e.g. ready-to-eat cereals. In WO 200205667, a glassy matrix is used to encapsulate an ingredient for fortification of food products with calcium. The calcium is first made into a slurry using a medium chain triglyceride while the glassy matrix comprises at least one oligofructose. Examples of food products are ready-to-eat cereals and yogurt. **Nestle** (WO 200200039) makes use of a glassy carbohydrate matrix for the encapsulation of flavours using a blend of polydextrose and lactitol and extrusion at 90-130 °C. Examples of flavours are tomato, chicken, beef and grilled flavours.

Cyclodextrin *encapsulated flavours for foodstuff, based on the reaction product of aldehyde, ammonia and sulfide, are claimed by* ***Nestle*** *(WO 200201967). New, non-hydroxylated cyclodextrin derivatives having at least one primary alcohol function substituted, and the application of cyclodextrin glucanotransferase to prepare cyclodextrins from solutions containing starch, dextrin, amylopectin and/or an amylose are patented by* ***Coletica*** *(GB 2362102) and* ***Nippon Shokuhin*** *(JP 2001327299), respectively.*

A number of patents appeared on ***gelatin*** for encapsulation purposes. **Opheim** (US 6346231) and **Bartz** (DE 20105126) both claim gelatin capsules with encapsulated fish oil and a flavour for oral administration. The Bartz patent also includes vitamin E and vitamin C to protect the fish oil against oxidation. Alternative, non-bovine and non-porcine gelatin for microcapsule formation is patented by **Cade** (US 20010024678, gelatin from fish, poultry or plants) and by **Consejo** (WO 200212408, gelatin from marine animal skins).

Liposomes or pro-liposomal formulations were mentioned several times in the patent literature. **Primacare** (EP 1138310 and 1138311) is using pro-liposomal formulations for the preparation of personal care products. Liposomes are further patented by **Kwailnara** (KR 2001083712) for cosmetic purposes and by **Coty** (WO 200213770) for the encapsulation of aqueous pineapple extract and the residue from the aqueous extraction of yogurt to be used in personal products.

Last but not least, patents were filed on the use of ***cellulose ethers*** (Henkel, DE 10015662), fractionated **yeast cell wall** (Takasago, EP 1159882) and a mixture of **co-crystallized polyol and hydrogenated maltodextrin** (Cunningham, US 20020011181) for the encapsulation of actives or to improve the texture of food products.

Transdermal

By Agis Kydonieus & Tapash K. Ghosh

The patents issued in the United States during 2001 are discussed in this review. There were 51 U.S. Patents published pertaining to transdermal delivery. Eleven of these patents were awarded to Lohmann, mainly in the areas of devices, manufacturing, and product applications. Following Lohmann were Alza with 8 patents, mainly in the fields of enhancers and electrotransport, and Acutek, Sontra, and Teikoku with 2 patents each.

The breakdown according to categories was methods/devices(18), enhancers(11), electrotransport(9), anti-irritant/countersensitizer(1), and methods/applications(12). The methods/applications patents differ from the methods/devices patents by the fact that the inventive spirit is mainly in the identification of a drug to be used for a specific transdermal therapeutic application.

Since our last update of a year ago, several commercial activities of interest have taken place. Ortho-McNeil Pharmaceuticals obtained U.S. approval of its Ortho Evra patch for contraception. The Ortho Evra patch contains ethinyl estradiol and norelgestromin and it is the first patch in this therapeutic area. Others are also working in the field, including Agile Therapeutics which has two Phase II clinical trials on-going.

In May 2001, Somerset Pharmaceuticals (50/50 joint venture between Watson and Mylan) filed a new drug application for EmSam (Selegiline) for the treatment of depression with expected approval in 2002. In April 2001, Watson filed a new drug application for an anticholinergic transdermal oxybutynin patch (oxytrol) for the treatment of overactive bladder with symptoms of urge incontinence, urgency and frequency of urination. In early 2002 the FDA requested additional clinical data, which Watson may already have from a separate phase IIIb trial.

Estradot (estradiol) from Noven, obtained European approval for the treatment of post-menopausal symptoms, and its U.S. equivalent Vivelle-Dot obtained approval for the treatment of osteoporosis in menopausal women. Novogyne (50/50 joint venture of Novartis and Noven) reaquired the rights to the Combipatch (estrogen/progestin patch) from Aventis and relaunched the product in the U.S.

(continued on page 19)

30th Annual Meeting and Exposition of the
Controlled Release Society

July 19-23, 2003 Glasgow, Scotland
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Consumer and Diversified Products Track

Program Chairs
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- Encapsulation and Release in Agriculture
- Flavors, Fragrances and Ingredients in Food, Personal Care, and Household
- Materials and Processing Technologies in Consumer Products
- Nutraceuticals and Cosmoceuticals
- Volatile-Matrix Interactions in Food and Personal Care Products

Bioactive Materials Track

Program Chair
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- Biological Barriers
- BioMimetic Materials
- Challenges for Oligonucleotide Delivery
- Dendrimers: Synthetic Chemistry to Microcontainers for Drug Delivery
- Engineered Materials
- Gene Therapy
- *In Vivo/in Vitro* Correlations; Animal vs Man
- Lipids: Where Next
- Micro and Nano Particles
- Modified Biopolymers as Solvents, Adhesives and Therapeutics
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- Tissue Engineering
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Abstract submission deadline: January 15, 2003

Visit www.controlledrelease.org for complete abstract submission instructions

SPOTLIGHT

ALZA: A Problem-Solving Approach to Better Pharmaceuticals

By Howard Rosen

Since its inception in 1968, ALZA Corporation has been the leading developer and manufacturer of drug delivery technology-based pharmaceutical products for the healthcare industry. ALZA was founded by Dr. Alejandro Zaffaroni to pursue his vision that the value of therapeutic compounds can be enhanced by optimizing their delivery into and within the body. ALZA partners with the world's leading pharmaceutical and biotechnology companies to develop products that are improving healthcare for millions of patients worldwide. ALZA drug delivery technology is derived from nine delivery platforms, and has been incorporated in 30 commercialized products marketed in more than 80 countries.

Today, ALZA's vision is to lead the next generation of drug delivery, by emphasizing a problem solving approach that extends to its leading oral, transdermal, liposomal and implant technologies and overall research and development efforts.

In 2001, ALZA merged with New Brunswick, New Jersey-based Johnson & Johnson, the world's most broadly based manufacturer of healthcare products, as well as provider of related services for consumers, pharmaceuticals, medical devices, and diagnostics markets. As a result of the merger, ALZA continues as an independent operating company, focusing on the development and manufacturing of pharmaceutical products based on novel drug delivery technology solutions for Johnson & Johnson and other companies in the global pharmaceutical industry.

Johnson and Johnson's acquisition of ALZA is an example of the promising future for drug delivery technology and drug delivery companies. Drug makers can benefit from delivery technologies such as those developed by ALZA because they often significantly enhance medications and can provide an extension on the patent life of a drug. In 2001, ALZA added approximately $700 million in sales to J&J's annual pharmaceutical sales of roughly $14.5 billion. Additionally, by joining the Johnson & Johnson family of companies, ALZA has gained access to one of the world's largest Research & Development networks. This is advantageous to both ALZA and its partners, by presenting a greater opportunity for technological advances that may benefit a wider range of product development opportunities.

Dr. Sam Saks

Sam Saks, MD, Company Group Chairman comments on what the merger has meant to ALZA's partnerships, "Because ALZA retains its core competencies in full-scale product development and manufacturing, our programs with partners outside of Johnson & Johnson remain very strong and will continue to grow. This merger makes us more attractive to partners interested in benefiting from ALZA's unique expertise in drug delivery, and our ability to find the right solutions for their product development needs."

Successful Partnerships Driven by Leading Technologies
Many of the world's leading pharmaceutical companies have worked with ALZA in the application of its delivery technologies for the development of leading therapies such as Concerta®, Procardia XL®, Ditropan XL®, NicoDerm® CQ®, and Duragesic®. ALZA's long history of successful partnerships is driven by a commitment to finding new and efficient ways to uncover innovative solutions while continuously improving our internal processes and research efforts.

"ALZA learned years ago that success requires both innovation and speed." Dr. Saks explained. "We have fine-tuned our decision-making, R&D, clinical, and manufacturing process using a Fast Cycle Time process that involves early management review, parallel track activities, minimal redundancy, enhanced intra-company communications, and a willingness to take measured risks to advance our timelines."

ALZA continues to evolve and build upon its leading oral, transdermal, implant and liposomal technologies. ALZA's recent innovation in oral technology includes L-OROS™ technology, designed for the delivery of liquid formulations. Advancements in the transdermal area include ALZA's Macroflux® technology, designed for the efficient delivery of proteins, peptides and other therapeutic macromolecules. In June of 2002, ALZA entered into a major collaboration with TransForm Pharmaceuticals. ALZA and TransForm will work together exclusively to develop and implement a proprietary, high throughput platform to enable the rapid and efficient identification of optimal formulations for future products incorporating ALZA's D-TRANS® technology. Within ALZA's liposomal research, ALZA is focusing on improved targeting and efficacy with STEALTH® technology. ALZA's implant technologies, ALZAMER® and DUROS® will concentrate on research for the improved delivery of macromolecules and biopharmaceuticals.

(continued on page 23)

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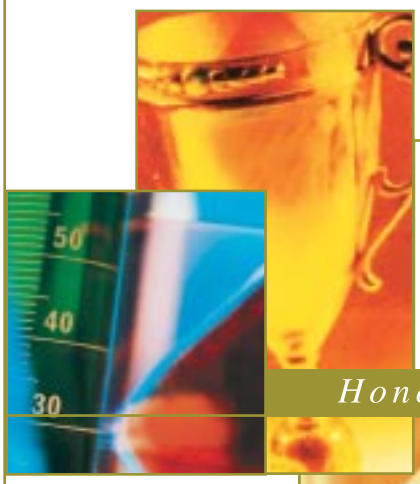

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Members Release Quite a Loud Voice

By Rosealee M. Lee

Do you know about the American Institute of Medical and Biological Engineering (AIMBE)? The Controlled Release Society (CRS) is a member of AIMBE, and as a CRS member, you are represented in the AIMBE Council of Societies.

CRS is dedicated to the future of the scientific community and its members. In my conversations with many members during the past year and a half, you have made it clear that one of our community's basic needs is to communicate outside our Society with policy-makers, funding agencies, and the public. In response to this need, CRS recently joined AIMBE. AIMBE is a non-profit society dedicated to national policy efforts in the medical and biological engineering arena.

CRS, along with approximately 20 other societies, form the AIMBE Council of Societies (COS), representing roughly 35,000 researchers worldwide. That number, working in unison, is quite a voice – quite a loud voice indeed when used for influencing lawmakers, government and funding agencies, and getting a strong scientific message out to the public.

I recently had the honor of being elected Chair of the National Affairs Committee for the COS. Together with Dr. Nicholas Peppas, Purdue University; Dr. Warren Grundfest, University of California, Los Angeles; and Subrata Saha, NYSCC at Alfred University, Alfred, New York, this newly formed committee represents COS societies and their members in matters of national affairs. The committee serves as a conduit for information, facilitator of resources, and liaison to enhance communication, representation, and funding in the areas of medical and biological engineering for all stakeholders (COS members, government agencies, practitioners, and the public).

Please take three minutes out of your day and visit the survey at www.controlledrelease.org (click on National Affairs Survey). This is your opportunity to be a quantifiable part of our community's solution for the future. The committee needs your input to identify national policy issues and concerns that you want addressed. Opportunities exist to visit regulatory agencies, draft position papers, write informational articles and technology updates. Your involvement is urgently needed.

Alexander Florence stated in a recent interview, ". . .we've got to do more to inform the public what we do. I don't believe that the public has been told that science isn't an exact art; that we don't have the answers. Sadly, there are more politicians who know nothing about science." Let's work together to change that! •

CRS Chapter News

By Duncan Craig

UKICRS January 2002 Meeting Oral Administration of 'Difficult' Drugs

UKICRS Chapter group photo

The annual one-day meeting of the UKICRS consisted of a symposium on the issue of oral drug delivery from molecules whereby effective absorption is a problem. We were fortunate in being able to bring together a highly renowned international group of speakers from both academia and industry, resulting in an oversubscription for attendance for the first time in the history of the organisation. The meeting was held at Astra Zeneca R&D, Charnwood on 17th January 2002, with the final delegate number being 140.

The meeting began with an overview from Professor Sandy Florence (School of Pharmacy, University of London, UK) who discussed some of the approaches that are currently under investigation to overcome poor absorption and solubility, including microemulsions, nanoparticles and solubilisation techniques. Professor Clive Wilson (University of Strathclyde, UK) discussed the latest approaches to imaging drugs and dosage forms within the GI tract, including a discussion of how gamma scintigraphy has allowed us to understand the post-ingestion fate of dosage forms and the possible future role of magnetic resonance imaging (MRI) for imaging non-radiolabelled material. The issue of drug absorption was addressed in detail by Professor Hans Lennernas (University of Uppsala), including a description of the use of the Loc-I-Gut instrument for perfusion experiments. This methodology has led to a number of surprising insights, and in particular has highlighted significant discrepancies between *in vitro* and *in vivo* dissolution behaviour. The theme of peptide drugs was addressed by Dr. Maurice Clancy (Elan Pharmaceuticals), who outlined some of the enzymatic processes associated with peptide and protein degradation and discussed the possible strategies that may be adopted to improve oral absorption. Professor Christos Reppas (University of Athens) gave a comprehensive overview of the rationale and practicalities underpinning the use of dissolution testing as a means of mimicking *in vivo* conditions, including an outline of the current thinking regarding the choice of dissolution media used to represent different regions of the gastrointestinal tract. The use of amorphous drugs in general and melt-extrusion technology in particular was discussed by Dr. John Hempenstall (GlaxoSmithKline), including consideration of the use of solid dispersions in amorphous polymeric carriers such as polyvinylpyrrolidone (PVP). The use of oral controlled release systems were reviewed by Dr. Ali Rajabi-Siahboomi (Colorcon), including an outline of the recent emphasis on developing novel strategies for defining specific release characteristics using geometric design technology. Finally, Dr. Paul Gellert (AstraZeneca) presented an industrial perspective of the issues associated with oral drug absorption, including consideration of the use of the biopharmaceutics classification system and the development issues associated with bringing such molecules on to the market, including the need to develop a reliable "best assessment" of the possibilities for successful development at an early stage.

Dr. Florence presents poster winner Andrew Baldwin with his award

Congratulations were expressed to the winners of the poster competition, John Murphy (Queen's University of Belfast) for his poster entitled " The use of micro-thermal analysis as a means of characterising particulate systems" and Andrew Baldwin (University of Nottingham) for his poster "Investigations into cationic liposome: DNA binding during lipoplex formation". Both winners received £500 and free registration for the CRS meeting in Seoul. •

Dr. Florence presents poster winner John Murphy with his award

OUR TECHNOLOGY

Use of *In vitro* Dissolution Testing Procedures for Veterinary Drug Products. Part I. The potential role of *in vitro* dissolution testing for products intended for multiple animal species

By Marilyn Martine, [1]Center for Veterinary Medicine, Food and Drug Administration, Rockville, Maryland
Charles Collins, [2]Palm Beach Atlantic College School of Pharmacy West Palm Beach, Florida

This is the first of two articles exploring the use of in vitro dissolution testing procedures for veterinary drug products. The articles are solely intended to be exploratory, seeking perspectives on questions facing both regulators and manufacturers of veterinary pharmaceuticals. In the first article the regulatory requirements to demonstrate product (formulation) bioequivalence for products intended for multiple animal species is considered together with the potential role of in vitro dissolution testing in this process.

When a drug product is approved for veterinary use, effectiveness and safety must be confirmed for each animal species included on the product label [Section 512 of the Food, Drug and Cosmetic Act]. The complexity of multiple species approvals continues throughout the life of a product; the potential impact of any post-approval change in product manufacture and formulation is considered for each of these target animal species [21CFR 514.8(j)]. In a similar manner, generic formulations need to be confirmed as bioequivalent to the pioneer for each target animal species appearing on the innovator's label [514.1 (d) (1) of Title 21 of the Code of Federal Regulations]. Examples of pre-approval and post-approval supplements received by the US Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) include switches from swallowed tablets to chewable dosage forms, changes in flavorants to increase product palatability, formulation and manufacturing changes to increase ease of use, changes in active bulk substance, and formulation or process changes to increase the efficiency of product manufacture.

The impact of requiring that product (formulation) bioequivalence be considered in multiple animal species is best appreciated from the perspective of the number of marketed products approved for use in more than one target species. In 1999, 31% of all oral dosage forms were approved for use in two or more target animal species (this does not include oral solutions for which a waiver would be granted). For parenteral formulations, 45% of all intramuscular (IM) and subcutaneous (SC) products were approved for use in two or more target animal species. Of these, approximately 25% were approved for use in three or more target animal species.

The combination of animal species included on any given veterinary product label reflects both a similarity of health (physiological) concerns and a comparability in the appropriate use of that dosage form for drug delivery. With regard to the latter, the matching of a dosage form to a target animal species reflects the relationship that exists between a drug's physico-chemical characteristics, the likelihood that the product will be consumed, the target species' gastrointestinal (GI) physiology, and husbandry practices or ease of administration. Oral suspensions, pastes, and syrups can be used in most animal species. Pellets and granules are generally used for drug delivery to horses and cattle, less frequently to swine, dogs and cats. The majority of feline and canine medications are formulated as suspensions, tablets or capsules. Tablets and capsules are rarely used to treat horses, cattle, or swine. In swine, the majority of oral medications are formulated for delivery in water and feed. Similar drug delivery methods are used in the treatment of chicken and turkeys. Thus, when two target animal species are included on the approved product label, the pairs most frequently observed are swine and poultry, horses and cattle (oral suspensions or use in feed), and dogs and cats (tablets, capsules and suspension).

Without reliable *in vitro* alternatives to *in vivo* drug absorption data, multiple *in vivo* bioequivalence/relative bioavailability studies would be necessary. This, in turn, poses several critical problems:

- Due to the relatively small profit margin associated with veterinary pharmaceuticals, the need to perform multiple bioequivalence studies may be economically prohibitive for all but the most lucrative of animal health products. Should sponsors consequently elect to forego pursuing these applications or formulation changes, this could have deleterious effects on the availability of cost effective and optimally formulated animal health products.

- When the number of studies is increased without adjusting the corresponding approval criteria, there is an increase in the risk of declaring truly equivalent products as being bioinequivalent (i.e., an increased risk of Type 1 error). For example, in a crossover study (n=24) where treatment means differ by only 5%, a 15% residual error in the rate or extent of absorption will result in a 20% risk of failing to successfully demonstrate product bioequivalence when the pioneer label indicates approval for product use in two target animal species. For more variable drugs (20% CV), this risk increases to 56%, even if the test and reference means are identical.

In August, 2000, the FDA's Center for Drug Evaluation and Research (CDER) finalized their guidance to industry titled: "Waiver of *In vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System". This guidance provides for the use of *in vitro* dissolution data as a surrogate for *in vivo* bioequivalence testing for those products containing highly soluble and highly permeable (Class I) compounds. Others have even suggested expanding waivers to some Class III (high solubility, low permeability) compounds (Blume and Schug, 1999). Similarly, CVM is interested in considering the feasibility of using *in vitro* dissolution data to support bioequivalence determinations and cross-species bioequivalence extrapolations, when appropriate.

The application of biopharmaceutics classification system (BCS)-based biowaivers in veterinary medicine necessitates an evaluation of whether or not drug permeability and solubility classifications are universally applicable. Unfortunately, given the current BCS definitions of solubility, (which considers the ability of a dose to dissolve within set volume of fluid) this may not be the case. Unlike human drug products, veterinary dosage forms are generally administered on a mg/kg basis. Moreover, due to the wide variation in body weight across breeds, genders and ages, a

multifold range of tablet strengths may be needed within a product line. However, it is uncertain as to whether or not gastric volume within a species varies in proportion to body size. In other words, let's assume we are dosing dogs at a rate of 10 mg/kg. In this case, a 10-kg dog would receive a 100-mg dose while a 20-kg dog would receive a 200-mg dose. To maintain a constant relationship between administered dose versus fluid volume for *in vivo* dissolution, the gastric volume would need to likewise double. The validity of a linear correlation between body size and gastric volume has not been verified. Given the nonlinear relationship often observed between body size and organ weight for other systems, such a relationship is unlikely.

With regard to permeability, drugs that are highly permeable in one animal species tend to be highly permeable in all animal species (Chiou and Barve, 1998; Clarke and Smith, 1984). Conversely, drugs that are absorbed via transcellular pathways or that exhibit site-specific absorption characteristics may exhibit species-specific permeability characteristics (Johnson, *et al.,*2001; Scharrer and Wolffram, 1987; Karasov, *et al.,*1985; Ferraris and Ahearn, 1983; Bijlsma, *et al.,*1995; He, *et al.,*1998). Nevertheless, interspecies differences in product bioavailability are most often the consequence of other variables such as GI transit time, *in vivo* dissolution, presystemic metabolism, physico-chemical interactions with gut contents, bacteria digestion, and site-specific differences in absorptive surface area. These differences have been extensively reviewed elsewhere (Martinez, *et al.,* 2002).

Even if the BCS classification of a compound would be confirmed in a particular target animal species, the question would remain as to whether or not *in vitro* dissolution test conditions and criteria must be tailored to the physiology of each particular animal species. In this regard, we need to distinguish between dissolution tests conducted for quality control (QC) purposes versus those conducted for supporting waivers of *in vivo* bioavailability study requirements. QC test procedures are used to evaluate product performance relative to its physico-chemical properties. These tests may not be used to assess the importance of a particular chemistry and manufacturing controls (CMC) change on *in vivo* absorption characteristics unless supported by appropriate *in vivo* information. The intent of these tests is to confirm interbatch consistency and product compliance with product specifications. Test specifications are based upon a reproducible and consistent environment that is designed to yield different results if the physical and/or chemical properties of the drug delivery system have significantly changed from that of the reference batch(es). The reference batch(es) is/are those used in biological testing with proven effect. In the conduct of QC test procedures, we are assuming that if some predetermined performance specifications are met, product batches will perform in a reliable manner when administered to patients. Thus, one set of conditions is applicable, regardless of target animal species. In this regard, it should be noted that, although a minor point, the temperature of the dissolution media should be adjusted to the temperature of the species for which the drug product is to be used. If several species are involved, a weighted mean value may be acceptable for QC purposes.

In cases where *in vitro* dissolution data are to be used to support *in vivo* product bioequivalence, it is uncertain as to whether or not the results from one set of dissolution test conditions or comparability criteria can be used to confirm product *in vivo* comparability across all target animal species. This leaves us with the question of whether *in vitro* test conditions and equivalence standards must be tailored to each species and if so, what modifications would be necessary? At least in part, the type of dissolution test criteria used to determine product comparability will depend upon the level of correlation being sought (CDER guidance, Dissolution Tests of Immediate Release Solid Oral Dosage forms, August, 1997):

Level A: Point-to-point relationship between *in vitro* dissolution and the *in vivo* input rate of the dosage form (i.e., *in vivo* dissolution). This is the highest category of correlation where *in vitro* data can be used to represent the complete plasma level curve.

Level B: Mean *in vitro* dissolution time compared to either the mean residence time or the mean *in vivo* dissolution time. This does not reflect the actual *in vivo* plasma level curve, since several curves may produce the same mean residence time values.

Level C: One dissolution time point (e.g., t50%, t90%, etc) is related to one pharmacokinetic parameter (e.g., AUC, CMAX, TMAX, etc).

While these types of correlation are likely to be highly species specific, a criterion similar to that used as the basis for many CDER BCS-based biowaivers may be appropriate for rapidly dissolving veterinary formulations. For example, we might consider using a criterion that no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using *U.S. Pharmacopoeia* (USP) Apparatus 1 at 100 rpm (or Apparatus 2 at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. Nevertheless, numerous questions still remain when considering the application of BCS concepts and IVIVC's to support veterinary drug approvals. We also believe that there may be some similar questions arising in human medicine when dealing with product equivalence in special populations, such as pediatric patients or individuals presenting with compromised GI physiology.

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(Patent, continued from page 10)

Here below some of the more interesting patents are discussed.

COUNTERSENSITIZERS/ANTI-IRRITANTS

Reduction of skin reactions caused by transdermal drug delivery (Alza) US6203817
A method is claimed for minimizing the irritation of non-zwitterionic drugs which are irritating when delivered transdermally, without reducing their flux through skin. For basic drugs with pKa between 6 and 12, a weak acid is added to control the pH within 3-6 pH units below the pKa of the drug. Weak acids disclosed include acetic acid, propionic acid, lactic acid and several others.

For acidic drugs with pKa between 2 and 6, a weak base is added to control the pH within 3-6 pH units above the pKa of the drug. Weak bases disclosed include ammonium, triethanolamine, lycine, morpholine, histidine, and several others.

ENHANCERS

Transdermal delivery system (Ben Gurion University) US6274166
A transdermal delivery system for proteins and peptides is disclosed which comprises the peptide or protein and mixtures thereof and an acceptable oxidizing agent. The oxidizing agent facilitates the permeation of the active agent, such as insulin, through the skin layers and into the blood stream. Pharmaceutically acceptable oxidizing agents include permanganate and silver protein.

Transdermal device for the administration through de-epithelialized skin (P.Svedman) US6264979
A device for the transdermal delivery of peptides and proteins is disclosed by delivering the drug through de-epithelialized skin. Proteins disclosed include vasopressin, human growth hormone, insulin, interferon, erythropoietin and calcitonin. Inhibitors of proteolitic enzymes, such as aminopeptidase, metalloprotease, carboxypeptidase and others, are described including bestatin, hosphoramydon, cholate and cholate analogs.

Device for enhancing transdermal agent flux (Alza) US6322808
A device to enhance the penetration of transdermally delivered drugs is presented, comprising a sheet member with a rigid support contacting and extending across the sheet member. The sheet member has a plurality of microprotrusions to penetrate the skin and allow the delivery of the drug through it and the rigid support allows for the transmission of the applied force in reproducible and reliable fashion to penetrate the skin with the microprotrusions.

Device for enhancing transdermal agent delivery and sampling (Alza) US6230051 and US6219574
A device is disclosed to treat the skin to increase drug permeability, comprising a sheet with plurality of microblades having a relatively sharp angled leading edge. The thickness of the blades is in the range of 7 to 100 micron.

Transdermal patch with attached pocket for controlled heating device (Zars, Inc) US6261595
A heating element attached to a dermal drug delivery patch is disclosed. The heating element provides controlled heat to the patch and skin and thus improves dermal drug administration.

Device for the transdermal delivery of diclofenac (3M) US6193996
A mixture of enhancers is described which is effective in increasing the permeation of diclofenac through skin. The enhancer mixture comprises an alkyl ester of an aliphatic monocarboxylic acid, an alkyl pyrrolidone and an alkane polyol.

Incorporating poly-N-vinyl amide in a transdermal system (Alza) US6248348
Poly-N-vinyl amide is shown to increase the permeation of drugs when used in conjunction with other enhancers. It is claimed that poly-N-vinyl amide also improves the adhesion and the stability of the patch.

Transdermal resorption of active substances from supercooled masses of levulic acid (Lohmann) US6264980
Levulic acid in a subcooled melt is claimed as an enhancer for the permeation of drugs through the skin. The only drug specifically claimed is buprenorphine base.

Transdermal compositions with enhanced skin penetration properties (Jenapharm/Lohmann) US6238284
A laminated transdermal device is claimed where the center layer contains two enhancers (one destructuring agent and one structuring agent) one of which is lipophilic with water absorption capacity of less than 1.4%. Families of enhancers are also claimed that contain alkyl radicals.

Device for transdermal electrotransport drug delivery of fentanyl and sufentanil (Alza) US6216033 and US6171294
An iontophoretic device is described for the delivery of fentanyl or sufentanil, from a hydrogel formulation, to induce analgesia in patients suffering from moderate to severe pain associated with major surgical procedures. The device is patient controlled and can deliver 20 to 100 mcgs fentanyl in up to 20 minutes and allows the patient to self administer medication up to 100 times per day.

Ultrasound enhancement of transdermal transport (Sontra Medical) US6234990 and US6190315
A method using the application of ultrasound is disclosed to increase the permeability of skin. An ultrasound beam, with frequency of 20 kHz to 2MHz, is applied to skin and it is geometrically configured to induce cavitation of the skin lipids. A two step process is also claimed whereby the ultrasound is initially applied to increase skin permeability and after removal of the ultrasound, transdermal transport is initiated.

Method for transdermal administration of GP IIb/IIIa antagonist (Hisamitsu) US6322550
A method of iontophoretic delivery is claimed for the administration of GP IIb/IIIa antagonist to prevent or treat angina pectoris, unstable angina, or coronary restenosis. The process comprises a first step where plural current applications are conducted continuously without interval, and a second step where plural current applications are conducted with an interval preceding each application. In each step the current density is progressively reduced in the subsequent application, to minimize side effects.

Electrically assisted transdermal method and apparatus for the treatment of erectile dysfunction (Genetronics) US6266560
Erectile dysfunction is treated by using electroporation, i.e. one or more electric pulses of sufficient strength and duration are applied to the penile shaft and gland to introduce enough vasoactive or androgenic medication, into the corporal cavernosum. Many vasoactive compounds are claimed including several prostanglandins. Androgenic compounds claimed include androsterone, testosterone, and DHEA.

(continued on page 20)

(Patent, continued from page 19)

Transdermal electrotransport delivery device including a cathodic reservoir containing a compatible antimicrobial agent (Alza) US6181963
An iontophoretic device is described where the cathode includes a cathodic electrode and a cathodic reservoir. The aqueous medium of the cathodic reservoir contains an electrolyte salt and cetylpyridinium salt, sufficient to inhibit bacterial growth in the aqueous medium. A process is also provided wherein when the electric current flows the transdermal permeation of the drug (fentanyl) takes place from the anodic electrode, and no cetylpiridinium is delivered through the skin.

Miniature valve for filling the reservoir of an apparatus for the transdermal administration of medicine (L.H.D.) US6247485
A miniature valve for filling the reservoir of an iontophoretic patch is disclosed. The valve comprises a) a substrate, b) a fuel charge and c) an electric resistor placed in contact with the fuel charge.

Predetermined electric energy sent to the resistor ensures the combustion of the charge and the opening of the passage by the local rupture of the substrate.

METHODS/DEVICES

Percutaneous delivery system (Soltec Research) US6211250
A liquid composition is presented for the transdermal delivery of active agents comprising the drug, a volatile solvent and a polymeric carrier which has the capability to modulate the release of the drug. The polymeric carrier consists of a hydrophilic and a hydrophobic polymer with the polymers and amounts selected to enable the modulation of the rate of delivery.

Hydrophilic polymers disclosed include hydroxypropyl cellulose, polyvinyl pyrrolidone and carbomer. Hydrophobic polymers include PVA, shellac, octylacrylamide and alkyl acrylates.

Enhanced transdermal anesthesia of local anesthetic agents (University of Georgia) US6299902
A novel topical composition is presented which exhibits improved absorption of an anesthetic such as lidocaine or tetracaine. The preparation contains a local anesthetic and at least two melting point depression agents. The formulation is a two-phase liquid composition that contains aqueous and oil phases, with the oil phase containing at least 70% lidocaine or other anesthetic.

Method of transdermal application of active substances at high constant dosage (Lohmann) US6280766
A method of transdermal treatment is described which is effective in delivering the drug in approximately constant rate, comprising the steps of a) applying a patch that has an effective period of several days and b) applying a second patch of the same product, before the expiry of half of the effective period of the first patch.

Skin-adhering pharmaceutical preparation, in particular transdermal therapeutic system for the release of 17-beta estradiol to the human organism (Lohmann) US6267982
A patch for the delivery of estradiol is presented which prevents crystallization of the estradiol in the patch. Estradiol unhydrate is dissolved in acrylate copolymer by drying, such as the concentration of estradiol is at least three times the saturation solubility concentration when measured at 95% rH. In addition the package is moisture tight and the air enclosed in the package is below 5%rH.

Composition for transdermal delivery of drugs (Novagent Oy) US6254883
A transdermal composition is claimed for the controlled release of a drug, which comprises a drug and an ion exchange group grafted to a fibrous web, made out of wool, cotton, polyethylene, etc., and an acceptable salt which is able to release the drug from the ion exchanger. The exchanger can be an anion or a cation such as a tertiary amine cation. The drug tacrine is disclosed as useful with this composition.

Transdermal drug delivery system (S. Feldman) US6207193
A transdermal formulation is claimed whereby the drug is encapsulated in a water soluble carbohydrate and the encapsulated drug is then suspended in cyanoacrylate ester capable of polymerizing by moisture. Upon contact with the skin, the cyanoacrylate ester is polymerized and thus controls the rate of drug release, and at the same time the moisture dissolves the carbohydrate allowing the release of the drug.

Useful carbohydrates include monosaccharides, such as glucose, mannose and galactose and disaccharides such as sucrose, lactose and maltose.

Transdermal compositions containing low molecular weight drugs which are liquid at room temperature (Noven) US6316022
A pressure sensitive adhesive transdermal device is disclosed which is based on a high shear resistant acrylic polymer, having a shear resistance greater than 50 hours (at 8 lbs; 70 deg C) and molecular weight between 600,000 and 1 million Daltons. The device also contains up to 40% of one or more drugs, one of which is a liquid at room temperature. No additives are included whose boiling point is higher than that of the liquid drug.

METHODS/APPLICATIONS

- Pain : Delivery of cannabis chemicals to minimize cancer pain (US6328992); Delivery of capsaisin to treat neuropathic pain together with an anesthetic to minimize side effects (US6239180); Delivery of doxepin, pergolide and bupropion together with guaifenesin to treat pain (US6290986).

- Depression : Delivery of bupropion to alleviate depression and also to minimize withdrawal symptoms due to nicotine craving (US6312716; US6280763).

- Hormone Replacement : Delivery of estradiol from an ethylcellulose base (US6274165); Delivery of a combination of hormones including estrogen, progesterone and testosterone (US6228852).

- Cardiovascular : Delivery of fenoldopam for the treatment of hypertention as well as impaired renal function (US6238693); Iontophoretic delivery of levosimendan or ropanedinitrile for treating heart failure (US6183771).

- Cancer : Delivery of acetylsalicylic acid for prophylaxis against cancer as well as antithrombotic therapy (US6264978).

- Allergy : Delivery of azelastine from a beeswax base as an anti-allergic treatment (US6299888).

Patent Watch Consumer & Diversified Products
January – June 2002 (200201 t/m 200240)
Jack Burger
Senior Scientist
Quest International
July 2002

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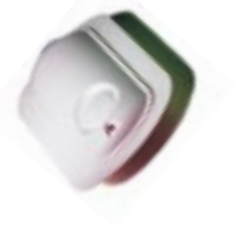

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InTheNews

Nanophase will Present at Nanotechnology Business Roadmap for Industry
Nanophase Technologies Corporation, a leader in nanomaterials and nanoengineered product solutions, will be participating in the "Nanotechnology Business Roadmap for Industry" conference to be held in Chicago, IL, USA October 14th -17th, 2002. The symposium featuring "a comprehensive survey of the six key nanomaterial technology platforms" will include panel discussions with industry experts and presentations from key executives providing a detailed view of their company's perception of the opportunities and challenges of nanotechnology.

According to Infocast, the conference producers, "this is the first conference organized for strategic and technology planning executives on the business opportunities and challenges of applying nanomaterials in their industries".

Dr. D. J. Freed, Nanophase's vice president for business development, is the invited speaker on Tuesday, October 15th on the "State of the Nanomaterials Industry: Players, Production Capabilities, Costs, and Future Trends". Dr. Freed's discussion will cover emerging trends in nanomaterials, availability of nanomaterials at commercial scale and economics, and the leading players in the nanomaterials business.

CardioNow Provides Filmless Image
Deaconess Billings Clinic (Billings, Montana), a VHA-affiliated medical center, has selected CardioNow to provide its Cardiac Image and Information Management Services (IMS) for the Cardiology Department. The conversion of the department's two cardiac catheterization laboratories and three echocardiography labs to filmless imaging and centralized secure digital DICOM storage will enable physicians to have immediate access to the results of patients' procedures, regardless of their location.

Rich Lundy, Director of Cardiac Services, said, "Deaconess Billings Clinic selected CardioNow for efficiency of service and for the global outreach capability using Internet-based technology of making cardiac images accessible."

"Conversion to centralized digital image management for both echocardiography and cardiac catheterization procedures will reduce the costs of managing patient's films and tapes. In addition to eliminating the costs of chemicals and film processing, our staff will not be spending their time making duplicate VHS tapes for referring physicians. We will start to see the beginning of the end of managing 10 years worth of cine film canisters and VHS tapes in film storage rooms where we no longer have space. All this is time consuming to manage," Lundy said.

"The biggest advantage that the CardioNow service will provide is that it will revolutionize the information outreach capabilities for physicians," Lundy explained. "We provide healthcare treatment to a predominantly rural constituency. The geographic region we serve is huge and the appeal of CardioNow's Internet-based technology is that it bridges the distance. All any referring physician needs is a personal computer and access to the Internet, and with proper authorization, there will be immediate access to their patient's cardiac records."

CardioNow's Image and Information Management Service will be integrated with Cedaron Medical Inc.'s cardiac care outcomes management system. The Cedaron product will consolidate patient data, reporting and billing functions with the ability to benchmark patient outcomes against national databases of the American College of Cardiology and the Society of Thoracic Surgery.

BioShield Technologies Receives Extended Patent Approval
BioShield Technologies, Inc. has received an approval from the U.S. Patent Office extending BioShield's AM500 antimicrobial, securing the rights to a broader array of applications and formulas. This new patent approval helps to solidify BioShield's positioning in the coatings industry and various other industries to control the growth of bacteria, mold, mildew and algae for both indoor and outdoor applications. The final patent filing and respective claims are anticipated to be issued as a U.S. Registered Patent within the next few months.

Deirdre Baker, BioShield's General Manager stated, "this new Patent approval contributes a great deal to our competitive advantage, creates new barriers to entry for our competition to participate in the antimicrobial and antibacterial industries, and further enhances and protects BioShield's intellectual property portfolio. The approval of this Patent further solidifies BioShield's position in the antimicrobial industry as having one of the broadest product lines that provide the benefit of being essentially non-toxic, water-based, non-leaching and having long-term effectiveness. Over the past five years, BioShield has invested over $20 million in product research and development, EPA registrations and patent filings and this latest milestone is another great example of the value that is created with BioShield's technology foundation."

Preservative-Free Influenza Vaccine for Pediatric Use Approved by FDA
The Food and Drug Administration (FDA) has approved licensure to Aventis Pasteur to market Fluzone® Preservative-free: Pediatric Dose, Influenza Virus Vaccine. For the first time, physicians have the option of offering a preservative-free formulation of influenza vaccine to infants aged six to 35 months.

Aventis Pasteur is producing a pediatric Fluzone vaccine to ensure continued public confidence in influenza vaccine for young children. The new vaccine will enable physicians to immunize infants, especially those considered high-risk, with a preservative-free influenza vaccine. In the near future, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) plans to consider strengthening its current encouragement to annually immunize healthy children aged six to 23 months. Children in this age group are at a substantially increased risk for influenza-related hospitalizations.

Due to the current scheduling of the influenza vaccine manufacturing process, Aventis Pasteur can provide only a limited quantity of pediatric Fluzone vaccine for the 2002-2003 season. However, Aventis Pasteur has the capacity to produce larger quantities of pediatric Fluzone vaccine for the 2003-2004 season should the ACIP expand its position on pediatric influenza immunization.

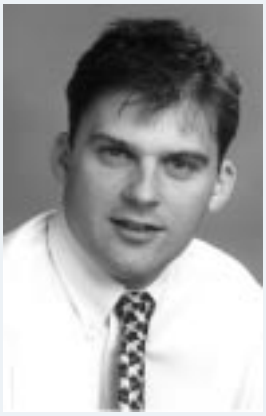
"Aventis Pasteur is pleased to provide physicians with the option of a preservative-free formulation of Fluzone vaccine to immunize infants aged six to 23 months," said Philip Hosbach, vice president, new products and immunization policy at Aventis Pasteur.

For the 2002-2003 influenza season, Aventis Pasteur's limited supply of pediatric Fluzone vaccine will be specially packaged for infants in pre-filled syringes (in a 0.25 mL presentation). Current production schedules anticipate that a limited quantity of pediatric Fluzone vaccine will be available for shipment in early to mid-November. Health care providers can be placed on a waiting list for pediatric

(continued on page 26)

PEOPLE ON THE MOVE

Kevin Shakesheff Honored at MIT's Award Ceremony



Professor Kevin Shakesheff

A University of Nottingham academic has been named among the world's top young innovators by a prestigious technology magazine.

Professor Kevin Shakesheff, 32, of the University's Tissue Engineering Group in The School of Pharmaceutical Sciences, has been chosen as one of the world's top 100 innovators under the age of 35 by Technology Review, the Massachusetts Institute of Technology's award-winning magazine.

The TR100, chosen annually by the magazine, consists of 100 young individuals whose innovative work in business and technology has a profound impact on today's world. Nominees are recognized for their contribution in transforming the nature of technology in industries such as biotechnology, computing, energy, medicine, manufacturing, telecommunications, and transportation.

Professor Shakesheff's research team is developing new methods of growing tissues in the laboratory. If this can be achieved then medical treatments for many incurable diseases will become possible. For example, the regeneration of liver, nerve, muscle, cartilage, and bone tissues using specialized and patented polymer templates that help cells grow into complex and functional tissues.

The clinical and commercial potential of the University work has led to the establishment of a new tissue engineering company called RegenTec Ltd. RegenTec is working with the pharmaceutical and tissue engineering industry to create new methods of drug screening and medical treatment.

Professor Shakesheff said: "I'm delighted that the work of my team in Nottingham has been recognized by such a renowned institution. I'm determined that our patents and ideas in tissue engineering and drug delivery will now become pivotal components of future technologies."

Professor Shakesheff is to be honoured during a conference and awards ceremony at MIT. The event, *The Innovation Economy: How Technology is Transforming Existing Businesses and Creating New Ones*, includes a full day of conference sessions and panel discussions followed by a gala awards ceremony.

Tomorrow's Scientific Entrepreneurs

University of Nottingham team are tomorrow's scientific entrepreneurs
A spin-out company from The University of Nottingham was named as the authors of the best business plan to commercialise British science.

Critical Pharmaceuticals Ltd has won the top prize of £25,000 in the Joint Research Councils Business Plan Competition - organised by three of the major British funders of science research. Judging took place at the Royal Society in London, with the prize awarded by Science and Innovation Minister Lord Sainsbury.

Critical Pharmaceuticals Ltd is a spin-out company from the Schools of Pharmaceutical Sciences and Chemistry at the University. Professor Kevin Shakesheff, who leads the company with Professor Steve Howdle, said: "The future of medicine is very exciting, with new treatments being devised to reverse arthritis, diabetes, obesity and other long-term diseases. The discovery of stem cells that can regenerate damaged tissues and the information derived from the human genome project is making these new medicines a reality."

"These new treatments do however contain extremely fragile molecules and cells, whose disease-curing properties can be destroyed before they leave the factory. The Critical Pharmaceuticals team has developed a new method of delivering the medicines to the patient that protects the drugs and cells. As a result, medicines that patients receive in the future will work better, and we can all share the remarkable opportunities to improve our long-term health".

The Joint Research Councils Business Plan Competition involves the Economic and Social Research Council, the Engineering and Physical Sciences Research Council, the Natural Environment Research Council and the Particle Physics and Astronomy Research Council.

The Nottingham team beat rivals from the universities of Newcastle, Manchester, Warwick, and Imperial College, London.

(Spotlight, continued from page 12)

Problem Solving Next Generation Drug Challenges
With leading technologies at its base, ALZA has recently placed an increased focus on exploring critical medical and therapeutic challenges that are fundamental to the future of the pharmaceutical and healthcare industry. ALZA's research efforts will not only include finding new applications for existing technology platforms, but also working with drug challenges and developing solutions to address them. Drug challenges associated with delivering biopharmaceuticals, and disciplines such as gastrointestinal, receptor, and skin biology; high throughput screening; protein and linker chemistry; material and formulation sciences; and biomedical engineering have become areas of emphasis at ALZA.

Dr. Michael Silber, Vice President of Research and Technology Development, comments, "We're establishing a clear vision to lead the next generation of drug delivery by working on products that are driven by medical, therapeutic, and commercial needs. Based on biology, pharmacology, and materials science, we'll develop hypotheses about the most innovative means of drug delivery. One of ALZA's primary goals is to get products to market faster than a traditional pharmaceutical or drug delivery company. This will continue to be one of ALZA's major strengths in order to maintain our competitive advantage."

Product after product, ALZA is not slowing down in its pursuit to lead the next generation of drug delivery. ALZA's leading drug delivery technologies and problem-solving approach to common drug challenges will be fundamental in maintaining successful partnerships that improve healthcare for patients worldwide.

CONSUMER AND DIVERSIFIED PRODUCTS

IMPORTANCE OF CONTROLLED RELEASE SYSTEMS IN THE CONSUMER AND DIVERSIFED PRODUCTS

By Jerome Barra

Most of the current CRS members are somehow related to the pharmaceutical field. However, the need to deliver a particular "active ingredient" to a specific site or in a controlled manner is also very relevant in an unbelievable number of other fields. This is what the "Consumer and Diversified Products" (C&DP) group is all about. For example, were you aware that controlled delivery systems are used in human and animal foods for flavors, in neutraceutical products for micronutrients, in agriculture for pesticides and nutriments, in home care and body care products for perfumes to mention a few? This year, at Seoul, posters and podium sessions were presented in the C&DP category along with the pharmaceutical applications of controlled release systems. These were a unique opportunity to meet people with other scientific backgrounds, see how they solved their release problematic, and get some good ideas to transpose to the pharmaceutical field. Next year, in Glasgow, similar opportunities will arise. Some examples of the current controlled release systems used in the "Consumer and Diversified Products" include matrix (spray-dried powders, extrusion products of different compositions, spray chilling, microspheres) and capsule (coacervates, coated particles, microcapsules, liposome) systems, as well as cyclodextrin, single or multiple emulsions.

Encapsulation of flavours in human and animal foods. Flavors are very complex and fragile (oxidation, volatile losses, chemical instability) products. They usually contain 5 to 50 different chemicals, each one exhibiting their own physicochemical characteristics. If one is missing or just unbalanced, the whole food product will be rejected by the final consumer. Industrial food products are submitted to harsh conditions during their manufacturing. For example, cookies are usually baked at high temperatures for several minutes, fermented yoghurts contain millions of living bacteria delighted to eat some flavour chemicals, hard-boiled candy and lollipop preparations involve boiling sugar syrup at high temperatures (Figure 1)… In all cases, encapsulation is needed to protect the flavor. However, the challenge is quite difficult as the system has to resist the harsh processing conditions but still has to release the flavor in the mouth of the consumer. In other applications, the flavor encapsulation system will have to sustain high moisture conditions during the shelf life of the product and release its content during baking in the final consumer's oven (*e.g.* frozen pizza). In addition to this protective role, flavor encapsulation systems can also be used to provide flavor bursts for example in chewing gum applications or to prevent chemical interactions with other sensitive materials (*e.g.* active ingredients in flavoured pharmaceutical products).

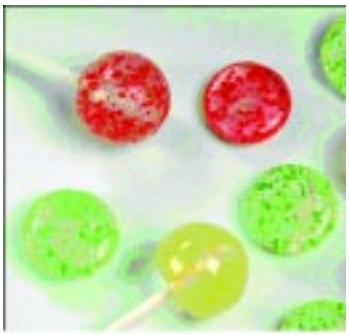


Figure 1. Protection of flavors during the industrial preparation on APV depositing lines of hard-boiled candies and lollipops using Flexarome® (Firmenich SA) particulate flavor delivery system. (picture: courtesy of APV Baker)

Encapsulation of micronutrients in neutraceutical products. Vitamins, co-enzymes, metallic ions can either be inactivated before consumption (degradation during processing), or during consumption (chemical degradation in the gastric juice or complexation). Encapsulation will provide protection while ensuring delivery in the most appropriate absorption zone, a problem very similar to those encountered in pharmaceutical applications. However, like the food market, the neutraceutical market is a very competitive market where high-pressure on prices imposes clear consumer benefits at constant on-cost compared to the non-encapsulated systems. Thus, encapsulation must involve cheap materials, low production cost, and a simple process.

Nutriments and pesticide in agricultural products. Sustained release systems able to release nutriment for agricultural fields over a 6 month period are now available on the market. These systems have to resist natural climatic conditions while ensuring a specific release profile. The use of encapsulated systems for pesticides decreases their negative impact on the environment significantly, reduces the quantity to be sprayed, and can target specific diseases. Via controlled release, chemicals can be delivered during a particular life cycle of the plant when the targeted pathogen agent is the most active. Burst release or sustained release can also be triggered by a variation of moisture after raining. Fish farming is also an area where specific encapsulation systems can be used. Here, the aim is to prevent nutriment losses by dilution and make the nutriment appealing for the desired fish.

Perfumes in home care and body care products. Similar to flavours in their complexity and fragility, perfumes can be encapsulated to protect their functionality. For example, soap manufacturing involves extrusion at relatively harsh conditions (encapsulated systems have to resist high shear conditions). Perfumes will have to resist such processes but still be perceived by the consumer washing hands. Shampoo is one of the most difficult challenges. Consumers expect a shampoo not only to smell nicely when opening the bottle but also to retrieve this fragrance on the hair afterwards. However, high hot-water flow used to rinse the hair is also very effective for removing all perfumes. If any perfume is left, it still has to sustain hot air flow from a fan! The same problem is encountered for liquid detergents in washing machines. Detergents are very aggressive chemicals, which can easily degrade the perfumes and their delivery systems, usually based on hydrophobic matrices. In addition to stability, these systems have to prevent permeation of the perfume during storage (not so easy as most perfumes are hydrophobic), to provide good homogeneity of the perfume in the final product (no sedimentation), and to avoid deposition and sticking on the washed substrate. In solid detergents (*e.g.* tablets for dishwasher), hydrophilic matrices are traditionally used as delivery systems. Challenges lay in high resistance to humidity upon storage, to compression during tabletting, and still to be able to deliver the perfume in a controlled fashion during the washing cycle. A nice impact upon package opening has to be delivered along with resistance to high dilution during washing and evaporation during drying and ironing.

These areas are just examples of the most common problems encountered by the formulation scientists involved in the C&DP area. Depending on the material to be controlled, the application targeted, and of course the legal and cost constraints, formulation scientists will use one, or more, specific delivery systems; a problem very similar to the one encountered by the pharmaceutical formulators. Certainly an area where C&DP and pharmaceutical formulation scientists can meet and profit from each other.

Journal of Controlled Release Highlights

By David Friend

The ISI Impact Factor is an important measure used to determine (rightly or wrongly) the relative ranking of journals in a particular field, such as pharmacology. The *Journal of Controlled Release* is judged accordingly. It is a tribute to the Editors of the *Journal* that the impact factor jumped from 2.15 in 2000 to 2.63 in 2001. Of journals publishing papers in the area of pharmaceutics, this number places it behind only *Pharmaceutical Research* (2001 Impact Factor of 2.80) and ahead of journals such as *Journal of Pharmaceutical Sciences* (2.12), *Biomaterials* (2.48), and *Journal of Drug Targeting* (2.19).

In the latest issue of the *Journal* (Vol. 82, no. 1), a paper by Yamamoto and coworkers describes the use of chitosan capsules containing 5-aminosalicylic acid to accelerate the healing of experimental colitis in rats. The biologic data correlated well with the delivery of drugs to the colon. Two papers describe the application of crosslinked high amylose starch as sustained release implants. This material has found extensive use as a matrix material for oral delivery but they are also well tolerated as implants. The first paper examines *in vitro* release of ciproflaxacin while the second paper examines release *in vivo*. Pack and coworkers describe a method for preparing monodisperse microspheres composed of poly(D,L-lactide-co-lactide-glycolide). Release kinetics could be controlled by mixing uniform microspheres of different sizes.

(News, continued from page 22)

Fluzone vaccine by calling 1-800-VACCINE (1-800-822-2463).

"Due to pediatricians increased awareness of the incidence of influenza virus infections in the first years of life, the ACIP and the American Academy of Pediatrics have encouraged the use of influenza vaccine for children aged six to 23 months," said Samuel L. Katz, Wilburt C. Davison professor of pediatrics and chairman emeritus of the pediatric department, Duke University Medical Center. "The availability of preservative-free influenza vaccine provides an alternative to parents and health care providers."

BioDelivery Sciences International, Inc. Receives NIH Grant

BioDelivery Sciences International has received a two year $600,000 National Institutes of Health (NIH) SBIR Grant to develop an oral form of a powerful HIV prophylactic/therapeutic vaccine with their patented Bioral™ drug delivery platform that is inexpensive, stable at room temperature, and is intended to induce protective, systemic and mucosal cell mediated immunity. The development will be conducted in collaboration with Biokeys Pharmaceuticals, Inc., an affiliated company, under a pre-existing research agreement. The BioDelivery team, led by Dr. Raphael J. Mannino (Principal Investigator of the grant) and Dr. Susan Gould-Fogerite, will work with Biokeys to develop the Biokeys Pharmaceuticals' EradicAide™ HIV prophylactic/therapeutic vaccine. BioDelivery will begin receiving the Grant in the fourth quarter in periodic installments totaling $300,000 per year, as work progresses.

Nearly 30 million people have died and 40 million people are infected with HIV worldwide as the epidemic continues to spread at a rapid rate. Effective vaccines to control the spread of the infection are desperately needed. Collaborators have identified short segments (peptides) of the surface protein gp160 of HIV that induce cell mediated immunity, and do not induce antibody responses. Cell mediated immunity, consisting of CD8+ T cells that kill virus infected cells and CD4+ T helper cells, is important in preventing and controlling HIV infection. These peptides are highly conserved; that is, present in many strains of the virus. Several peptides have also been identified as targets of CD8+ cells in long term non-progressors, individuals who control HIV virus replication more effectively and remain healthy for many years.

Monkeys immunized by injection with Biokeys Pharmaceutical's cocktail of six peptides (EradicAide™) were able to better control infection following challenge with a pathogenic strain of chimeric SHIV (recombinant Simian immunodeficiency virus with the surface protein from HIV). The immunized monkeys had lower levels of circulating virus (in some cases undetectable), maintained higher CD4+ helper T cell levels, and remained healthy for as long as three years. It is important to remember that no therapeutic vaccine completely prevents infection. The goal of vaccination is to induce immune responses that will reduce the infection, protect from serious consequences, and hopefully allow clearance of the organism.

BioDelivery scientists are collaborating with Biokeys to produce a version of the vaccine that can be given orally. The novel adjuvant/immunomodulating agent to be used is an extract of the envelope glycoproteins and lipids from parainfluenza type 1, Sendai virus derived envelope (SDE). This adjuvant is a potent stimulator of cell mediated immunity and has been shown to be safe in multiple animal studies and in a two year, ten patient, clinical trial of an autologous, therapeutic HIV vaccine sponsored by BioDelivery. The delivery vehicles to be used are BioDelivery's patented cochleates.

CellFactors Lead Product Skeletex™ Successfully Induces New Bone Formation

CellFactors, novel human cell-derived bone-regeneration product Skeletex™ has successfully demonstrated its ability to induce the spontaneous formation of new bone. These positive results were seen in an *in vivo* preclinical model, which is a key test used by the orthopaedic industry, academics and regulators, to assess the true effectiveness of bone-inducing agents.

Several leading orthopaedic companies are currently evaluating Skeletex™ with a view to licensing the material for orthopaedic uses, such as spinal fusion and prosthetics, an estimated global market of $12.5 billion annually. Bone-inducing agents have been proven to add significant clinical benefits when used with these products.

CellFactors intends developing Skeletex™ itself for dental applications, such as implants and periodontal disease. Following the results of this study, CellFactors expects to enter Skeletex™ into human clinical trials in this area in 2003.

"Skeletex™ is one of a new class of human tissue-engineered therapeutic products. These products will not be regulated as medicines, which means that the development timelines are not equivalent to those for conventional therapeutics. The clear advantage here is that the route to market for such a product, assuming all hurdles are cleared, could be much reduced." •

eventcalendar

who...what...where...when

How to Design and Implement Effective Stability Programs for Biotechnology Products
November 18-19, 2002
Research Triangle Park, NC, USA
rclark@iirny.com
www.pharmatraining.org
ph: 212-661-3500

IIR Potent Hazardous Compounds
November 18-19, 2002
Hyatt Regency New Brunswick
New Brunswick, NJ, USA
register@iirusa.com
www.iirusa.com/potentcompounds
ph: 212-967-0097

Cold Spring Harbor Biotechnology Conference on Tissue Engineering
November 21-24, 2002
Cold Spring Harbor, NY, USA
tuanr@mail.nih.gov
http://meetings.cshl.org/2002Tissue.htm
ph: 301-451-6854

Strategic Research Institute
Biomarkers Speeding Drug Discovery and Development
December 5-6, 2002
Hilton Harbor Island Hotel
San Diego, CA, USA
skuperberg@srinstitute.com
www.srinstitute.com/cs205
ph: 888-666-8514

Institute for International Research
6th Annual Pharmaceutical Stability Programs
December 9-11, 2002
Crown Plaza Center City Philadelphia
Philadelphia, PA, USA
skohen@iirusa.com
www.iirusa.com/stability
ph: 888-670-8200

UWEB
Gels, Genes, Grafts and Giants: Transitioning into the 21st Century
December 17-20, 2002
The Westin Maui, Ka'anapali Beach
Maui, HI, USA
info@uweb.engr.washington.edu
www.uweb.engr.washington.edu
ph: 206-616-9716

Center for Biomedical Continuing Education
5th International Symposium on Anti-Angiogenic Agents Recent Advances & Future Directions in Cell Biology & Clinical Research
January 30-February 2, 2003
Hyatt Regency La Jolla
San Diego, CA, USA
symposiua@thecbce.com
www.thecbce.com/futureprograms.asp
ph: 972-929-1900

MN Optometric Association Winter Symposium
February 1, 2003
Sheraton West
Minnetonka, MN, USA
info@MNEyedocs.org
www.MNEyedocs.org
ph: 800-678-8232

University of Miami & Sylvester Cancer Center
2003 Miami Nature Biotechnology Winter Symposium
February 1-5, 2003
Radisson Deauville Resort Hotel
Miami Beach, FL, USA
mnbws-biochem@miami.edu
www.med.miami.edu/mnbws
ph: 305-243-3597

Orthopaedic Research Society
49th Annual Meeting
February 2-5, 2003
New Orleans, Louisiana, USA
ors@aaos.org
www.ors.org

Controlled Release Society
Winter Symposium & 11th International Symposium on Recent Advances in Drug Delivery Systems
March 3-6, 2003
Grand America Hotel
Salt Lake City, Utah, USA
director@controlledrelease.org
www.controlledrelease.org
ph: +1-763-512-0909

GRIBOI
13th Interdisciplinary Research Conference on Biomaterials
March 14-15, 2003
Baltimore, MD, USA
www.jhbmc.jhu.edu/griboi03

PTEI
Engineering Tissue Growth International Conference and Exposition
March 17-20, 2003
Westin Convention Center
Pittsburgh, PA, USA
pcantini@ptei.org
http://etg-online.com
ph: 412-395-4202

Society For Biomaterials
29th Annual Meeting
April 30-May 3, 2003
Reno Hilton
Reno, NV, USA
member@biomaterials.org
www.biomaterials.org
ph: 763-512-0909

American Society for Artificial Internal Organs
49th Annual ASAIO Conference
June 19-21, 2003
Hilton Washington
Washington DC, USA
info@asaio.com
www.asaio.org
ph: 561-391-8589

Controlled Release Society
30th Annual Meeting and Exposition
July 19-23, 2003
Glasgow, Scotland
register@controlledrelease.org
www.controlledrelease.org
ph: 763-512-0909

BMES
2003 BMES Annual Fall Meeting
October 1-4, 2003
Renaissance Nashville Hotel
Nashville, TX, USA
www.bmes.org

OsteoArthritis Research Society International (OARSI)
2003 World Congress on Osteoarthritis
October 12-15, 2003
Berlin, Germany
oarsi@oarsi.org
www.oarsi.org
ph: 1-202-367-1177

Surfaces in *Biomaterials* Foundation presents BioInterface 2003
October 22-24, 2003
Savannah Marriott Riverfront
Savannah, GA, USA
member@surfaces.org
www.surfaces.org
ph: 763-512-9103

Robert S. Langer, MIT
7th US-Japan Symposium on Drug Delivery
December 14-19, 2003
Westin Maui, Kaanapali Beach
Maui, Hawaii, USA
cjbeal@mit.edu
http://web.mit.edu
ph: 617-258-5290

Australian Society For Biomaterials
7th World Biomaterials Congress
May 16-21, 2004
Sydney Convention and Exhibition Centre
Sydney, Australia
biomaterials@tourhosts.com.au
www.tourhosts.com.au/biomaterials
ph: +612-9262-2277

Surfaces in *Biomaterials* Foundation presents BioInterface 2004
October 27-29, 2004
Wyndham Baltimore Inner Harbor
Baltimore, MD, USA
member@surfaces.org
www.surfaces.org
ph: 763-512-9103

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