CONTROLLED RELEASE SOCIETY

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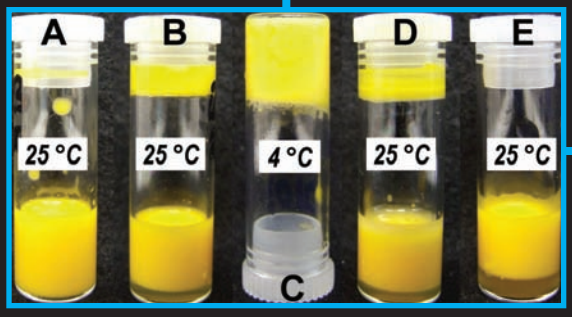
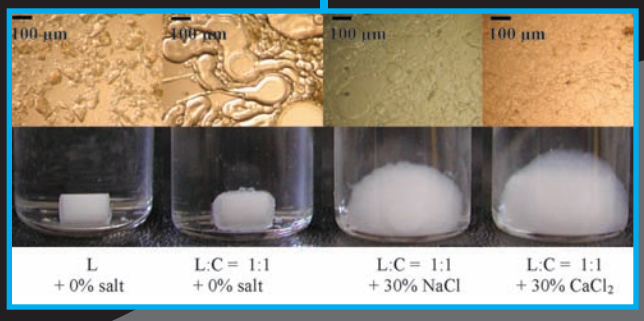
NEWSLETTER





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inthisissue

On the cover –

Robert S. Langer being congratulated by President George W. Bush. Photo credit: Ryan K. Morris, National Science and Technology Medals Foundation

Left to right: Dr. Shen Luk (Molecular Profiles), Lord Mayor of Nottingham Mohammed Munir, The Queens Lieutenant, and Prof. Martyn Davies and Dr. Nikin Patel (Molecular Profiles), receive the Queen's Award. Photo courtesy of Molecular Profiles

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

FROM THE Editors

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

Roderick B. Walker

It seems like it was only yesterday that we were submitting abstracts for the meeting in Long Beach, California, and here we are already at the end of 2007; and a busy and successful year it has been for the CRS and its members.

In this issue of the *Newsletter* you will be inspired through interviews of two prominent members of the CRS—Bob Langer, who received the National Medal of Science in the United States, and Martyn Davies, whose company Molecular Profiles won the Queen's Award for Enterprise this year. It is the potential to interact, meet, collaborate with and get advice from individuals of this calibre that make the CRS the unique organization it is; certainly, their achievements have given the CRS greater prominence in the field of drug delivery.

There are enlightening articles in which lipid-based protein delivery and the evaluation of these technologies are described, as well as an interesting approach to optimizing transdermal delivery using diffusion modelling. The Spotlight column highlights Delcath Systems, Inc., wherein a unique approach to the delivery of high doses of chemotherapeutic agents has been made possible by use of their new technology. The potential importance of omega-3 fatty acids in reducing cardiovascular diseases is known, and as the Western diet content of these important compounds is below the recommended, dose supplementation is necessary. The nature of these molecules necessitates the use of techniques such as microencapsulation to produce stable food products. As usual the In the News column clearly indicates that pharmaceutical and drug delivery technology research is healthy and vibrant and that there is one constant in this arena and that is that there is always change.

There are many opportunities in the CRS for you as members to participate and share ideas. The current and future success of the CRS is directly related to the enthusiasm and interest of its members and in this respect we encourage members to participate actively by volunteering to serve as abstract reviewers or on a committee. We also encourage you as members to submit articles of interest, reports, or news for publication in the *Newsletter*.

The abstract deadline for the 35th CRS Annual Meeting in New York in July 2008 is January 31, 2008, and submissions are now open. Submit your abstracts to ensure that the 2008 meeting is the biggest and best meeting of the CRS yet. Six plenary speakers from the United States, Nigeria, and Singapore have been identified for what promises to be an exciting conference. Three top-quality Educational Workshops in which the "Delivery of Biologics with Novel Polymeric Constructs," "Oral Drug Delivery: Challenging Patient Groups," and "Strategies to Advance the Bioavailability of Low Solubility Drugs" will precede the conference. I hope to see you all in New York.

All that remains is for me to wish all our members a peaceful and pleasant holiday season. Take care, travel safely, and may 2008 bring all you and your families wish for. ■

Susan Cady
CRS President

From the President

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

As I mentioned in the last *Newsletter*, the Board of Directors and senior staff members are working on the five-year CRS strategic plan. We will be posting the plan on the CRS website after our next face-to-face meeting November 10 and 11. The BOD set six high-level goals, and we have been developing objectives to meet these goals, establishing timelines and benchmarks, and assigning responsibilities to CRS people (BOD members, staff members, BSA, committees, etc.). We will be reviewing and refining this plan at our next BOD meeting. It has been a while since the BOD spent dedicated sessions on strategic planning, and we all believe that the time is well spent as we look to the future of our organization.

The overall goals that were defined during the September meeting are

1. Promote high-quality research and development in the science, technology, and innovation of delivery of bioactives
2. Maintain and strengthen our professional organization
3. Become the primary information resource for the science, technology, and innovation of delivery of bioactives
4. Foster professional growth and development of members
5. Promote awareness of the science of delivery of bioactives
6. Ensure that the science of delivery of bioactives provides a benefit to society

As the BOD goes forward with more focus provided by the strategic agenda, we will rely on staff and CRS members to work on the assortment of operational tasks. In addition, we will be charging some of our committees with strategic objectives. For example, the Planning and Finance Committee has been asked to develop the CRS strategic financial plan to match the strategic plan. As part of this plan, the role of the Committee and the role of the BOD will be established. As CRS looks to diversify and build several new revenue-generating programs, we will need to make financial decisions that take into consideration the strategic plan and strategic financial plan.

It is the role of the BOD to make strategic decisions on which of the new programs CRS should move forward with and when. Then, specific committees and staff will be given the charge and budget to create strategies that make the new program happen.

We will be relying on the various committees and staff to provide the Board with enough analysis so the BOD can make these strategic decisions. Would you like to serve on one of the committees and participate in some of these activities? If so, please contact me or Jody Grider at the CRS office.

We are also starting to move forward with the CRS publishing initiative. I am pleased that Mike Rathbone has agreed to be the chair of the Book Publishing Committee. We look forward to the first of what we hope will be many new works coming from our CRS series. If you have suggestions, please contact Mike with your ideas.

One of my tasks for the coming year is to get the CRS Foundation established. One of the first initiatives of this program is to establish a scholarship in the memory of Joe Robinson. Randy Mrsny and Kinam Park have graciously agreed to spearhead this new effort. They are charged with raising the funds and designing the procedures for the Review Committee by the 2008 CRS Annual Meeting in July. I hope to roll out the announcement of the first award at the NYC meeting. Please contact one of us with any ideas you have for this program. Of course, your contribution toward the scholarship fund is also welcome. Please contact CRS Headquarters for more details.

The CRS Annual Meeting Program Committee and staff are already working on the plans for the 35th CRS Annual Meeting & Exposition to be held in New York City. I am excited that Past Presidents Kinam Park and Bob Langer have agreed to be the keynote speakers for the banquet. Our 35th anniversary meeting will be special. Mark your calendars now for the meeting (July 12–16, 2008) and watch the website for more details and registration information.

I would like to hear from you if you have comments or suggestions. After all, this is your society. What initiatives would you like or want to see?

Happy holidays,

Susan M Cady

Susan Cady ■

Robert S. Langer Awarded National Medal of Science

By Bozena Michniak-Kohn, Ph.D.
Rutgers–The State University of New Jersey
Ernest Mario School of Pharmacy, U.S.A.

Robert S. Langer

In July 2007 the White House announced that President George W. Bush would present the National Medal of Science to Robert S. Langer. The National Medal of Science was established in 1959 to honor individuals who are "deserving of special recognition by reason of their outstanding contributions to knowledge in the physical, biological, mathematical or engineering sciences." In 1980 Congress expanded this recognition to include the social and behavioral sciences.

Dr. Langer is one of 13 Institute Professors at MIT, runs the largest biomedical engineering research laboratory in the world, and has more than 950 published papers and 600 issued and pending patents worldwide. Dr. Langer's patents have been licensed or sublicensed to more than 200 pharmaceutical, chemical, biotechnology, and medical device companies; a number of these companies were launched on the basis of these patent licenses. He also served as a member of the U.S. Food and Drug Administration's Science Board, the FDA's highest advisory board, from 1995–2002 (chair 1999–2002).

During the 1970s Dr. Langer developed polymer materials that permitted large molecular weight molecules to pass through membranes in a controlled manner. His work is at the interface of biotechnology and materials science. A major current focus is the study and development of polymers to deliver drugs, particularly genetically engineered proteins, DNA, and RNAi, continuously at controlled rates for prolonged periods of time.

Dr. Langer has received more than 150 major awards. In 2002, he received the Charles Stark Draper Prize, considered the equivalent of the Nobel Prize for engineers and the world's most prestigious engineering prize, from the National Academy of Engineering. He is also the only engineer to receive the Gairdner Foundation International Award; 68 recipients of this award have subsequently received a Nobel Prize. Among the numerous other awards Langer has received are the Dickson Prize for Science (2002), Heinz Award for Technology, Economy and Employment (2003), the Harvey Prize (2003), the John Fritz Award (2003) (given previously to inventors such as Thomas Edison and Orville Wright), the General Motors Kettering Prize for Cancer Research (2004), the Dan David Prize in Materials Science (2005), and the Albany Medical Center Prize in Medicine and Biomedical Research (2005), the largest prize in the United States for medical research. In 2006, Dr. Langer was inducted into the National Inventors Hall of Fame. In 1998, he received the Lemelson-MIT prize, the world's largest prize for invention for being "one of history's most prolific inventors in medicine." In 1989 Dr. Langer was elected to the Institute of Medicine of the National Academy of Sciences, and in 1992 he was elected to both the National Academy of Engineering and the National Academy of Sciences. He is one of very few people ever elected to all three U.S. National Academies and the youngest in history (at age 43) to have received this distinction.

Forbes Magazine (1999) and *Bio World* (1990) have named Langer as one of the 25 most important individuals in biotechnology in the world. *Discover Magazine* (2002) named him one of the 20 most important people in this area. *Forbes Magazine* (2002) selected Langer as one of the 15 innovators worldwide who will reinvent our future. *Time Magazine* and CNN (2001) named Langer as one of the 100 most important people in America and one of the 18 top people in science or medicine in America. *Parade Magazine* (2004) selected Langer as one of six "Heroes whose research may save your life." He has served, at various times, on 15 boards of directors and 30 Scientific Advisory Boards of such companies as Wyeth, Alkermes, Mitsubishi Pharmaceuticals, Warner-Lambert, and Momenta Pharmaceuticals. Dr. Langer has received honorary doctorates from Yale University, ETH (Switzerland), Technion (Israel), the Hebrew University of Jerusalem (Israel), the Universite Catholique de Louvain (Belgium), the University of Liverpool (England), the University of Nottingham (England), Albany Medical College, The Pennsylvania State University, Northwestern University, and Uppsala University (Sweden). He received his B.S. degree from Cornell University in 1970 and his Sc.D. from the Massachusetts Institute of Technology in 1974, both in chemical engineering.

Bob Langer is a remarkable person—and one who responds within minutes to e-mails from his Blackberry. I conducted an interview with Dr. Langer in September:

Q *What was the specific scientific achievement that triggered the receipt of the National Medal of Science?*

A The White House said "For his revolutionary discoveries in the areas of polymeric controlled release systems and tissue engineering, and synthesis of new materials that have led to new medical treatments that have profoundly affected the wellbeing of mankind."

Q *What are some current updates on the status of Gliadel?*

A My understanding is that more and more patients are using Gliadel. Dr. Henry Brem, Chief of Neurosurgery at Johns Hopkins, has mentioned that 1/3 of patients with brain cancer are using Gliadel (in many cases, the tumor has spread too far, so Gliadel is not used in those cases), and this number continues to increase based on its success.

Q *Can you describe briefly your impressions from the reception/ceremony in the White House?*

A I was very excited to be at the White House. It was the first time I'd ever been there. It was quite a privilege to be there

and was exciting for both me and my family to meet the President and talk to him, and the Secretary of State, and other individuals there.

Q *Can you make a few comments on your own career development, and perhaps tell us how you moved from graduate student status to essentially becoming a tissue engineer?*

A In my career, a big focus and important area of change was my postdoctoral experience. I went from being a chemical engineer as a graduate student to working in a surgery department as a postdoc. That exposed me to many things, including individuals like Jay Vacanti, and medical problems that made me think about strategies that might enable tissues to be engineered someday.

Q *What are the particular ingredients for your spectacular success as a scientist?*

A A good education, but also great role models like Judah Folkman, and great collaborators like Nick Peppas, Henry Brem, and Jay Vacanti, and having wonderful students and postdocs, which I've been fortunate to have at MIT.

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

A I think the discovery that it was possible to release macromolecules from polymers led not only to new delivery systems, but to the isolation of the first angiogenesis inhibitor.

Q *How do you balance work and family life?*

A My wife tells me I should be home at 7 every night, and I try to do that. Even though I travel, I'm never gone very long. For example, 5 years in a row I've had to go to Israel for different reasons, and each time I went there, I just flew there and back without using a hotel. I can take a flight that gets me there in the morning and take a 1 a.m. flight back. So I'm never gone very long.

Q *Could you recommend a publication that exemplifies your work from your extensive bibliographic list that would be particularly noteworthy for our CRS readers to read?*

A Perhaps our paper in *Accounts of Chemical Research* in 2000. It's volume 33, pages 94–101.

Q *What advice would you give to our young graduate students as they embark on their scientific careers?*

A I would tell young graduate students to get an excellent education, learn fundamentals, get exposed to ideas—all kinds of new ideas. And, talk to people about what their careers have been like—what did they like and what didn't they like.

Q *You have been involved with the Controlled Release Society for some time now, and what is your current perspective on the field of controlled release?*

A My perspective is that the field of controlled release has made enormous contributions. I remember chairing a Controlled Release Society meeting in the year 1982, and there were 20 talks on pharmaceutical drug delivery. Now, there are hundreds, if not thousands, of presentations at these meetings. It's been incredibly exciting to see the field grow and make so many contributions.

Q *Do you think that the controlled release area is a mature science and that most of the groundbreaking inventions have already been made?*

A I think the field of controlled release is a mature science. On the other hand, I think there are still plenty of groundbreaking inventions to make. So, even though there has been a lot of progress, I think that there are even more kinds of important things that can be done.

Q *What are your thoughts on the issues of nanotoxicity and impact on the environment (if any) as a potential threat to the success of nanotechnology in the medical arena?*

A I personally don't think that there are a lot of things to worry about with nanotoxicity as far as drug delivery goes. Liposomes are a good example of a drug delivery nanotechnology that's been around for some time, and to my knowledge liposomes have never caused particular toxicity problems just because the particles are so small.

Q *In what area do you think the next scientific breakthroughs will occur?*

A I think delivery of genetic materials like SiRNA and DNA, drug targeting to specific cells, non-invasive delivery of complex molecules, the development of MEMS technology for controlled release, and cell delivery.

Q *Skin was the first organ to be tissue engineered. Do you think we have more work to do in this area, and if so, what should be done from the clinical perspective?*

A I think we have much more work to do in this area. I think it's very exciting. I think there are many new tissues left to be engineered, for which there is a lot of work going on. These include cartilage, bone, intestine, liver, spinal cord, vocal cord, heart, and many others. The key issue from a clinical perspective is to move these technologies forward and to come up with the scientific advances that will move them from the laboratory to clinical trials in patients. This will involve research in cell biology, materials science, immunology, surgery, and other areas.

Selected Publications

Langer, R. Perspectives: Drug delivery—Drugs on target, Science 293: 58-59 (2001).

Kost, J, Mitragotri, S, Gabbay, R, Pishko, M, Langer, R. Transdermal monitoring of glucose and other analytes using ultrasound, Nat. Med. 6: 347-350 (2000).

Niklason, L, Gao, J, Abbot, W, Hirschi, K, Houser, S, Marini, R, Langer, R. Functional arteries grown *in vitro*, Science 284: 489-493 (1999).

Santini, J, Cima, M, Langer, R. A controlled-release microchip, Nature 397: 335-338 (1999).

Langer, R. Drug delivery and targeting, Nature 392 (Suppl.): 5-10 (1998).

Edwards, D, Hanes, J, Caponetti, G, Hrkach, J, Ben-Jebria, A, Eskew, M, Mintzes, J, Deaver, D, Lotan, N, Langer, R. Large porous aerosols for pulmonary drug delivery, Science 276: 1868-1871 (1997). ■

Molecular Profiles Wins Queen's Award for Enterprise 2007

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

Martyn C. Davies

Earlier this year, Molecular Profiles was awarded a Queen's Award for Enterprise in the Continuous Innovation and Development category. The award recognized the company and its complete range of services as one of the United Kingdom's most innovative during 2007. The Queen's Awards for Enterprise are the United Kingdom's most prestigious awards for business performance. They recognize and reward outstanding achievement by U.K. companies.

The Queen's Award for Enterprise recognized Molecular Profiles' unique contract research services, which encompass the company's knowledge and skills in advanced analytical techniques. The services can be broadly categorized into three key areas: formulation support (including pre-formulation and product R&D); rapid problem solving (during pre-formulation right through to manufacturing); and patent and litigation support.

Molecular Profiles is also a leader in the provision of innovative contract research services to the pharmaceutical and biomedical sectors worldwide. Their services include nanoscreening technology for predicting the ease of development of a new medicine, a deformulation service for identifying problems with a product down to the nanoscale, and advanced imaging for viewing and optimizing the internal structure of products.

In July of this year the Queen presented the award personally to Martyn C. Davies, chair and a founder of Molecular Profiles; Nikin Patel, CEO of Molecular Profiles; and Claire Madden-Smith, commercial director of Molecular Profiles, at a ceremony at Buckingham Palace.

Prof. Davies has supervised over 60 Ph.D. students to the successful completion of their degrees, many of whom have gone on to postdoctoral fellowships and to hold prominent posts within the pharmaceutical, chemical, polymer, and diagnostics industries, and one has moved successfully into pharmacy management. The School of Pharmacy was presented the Queen's Award for Enterprise in the Innovation category in April 2007. Prof. Davies has published more than 300 scientific papers and reviews.

Prof. Davies obtained his Ph.D. degree in pharmacy at the Chelsea School of Pharmacy, University of London. He joined the School of Pharmacy in Nottingham in 1985 and was promoted to a personal chair in 1996. He served as the head of the School of Pharmacy from 2000 to 2003, and he has served as scientific secretary of the Controlled Release Society. He is a Fellow of the Royal Pharmaceutical Society and a Fellow of the Royal Society of Chemistry.

I asked Prof. Martyn Davies about Molecular Profiles, winning the Queen's Award, and his career in controlled release science.

Q *What prompted the presentation of the Queen's Award for Enterprise to Molecular Profiles?*

A The award has been given in recognition of our continued innovation in our analytical work. The award is made each year by the Queen, on advice from the Prime Minister, who is assisted by an advisory committee made up of representatives from government and industry. The scrutiny and thoroughness of the process is considerable and our Commercial Director, Dr. Claire Madden-Smith, and her team did an amazing job fielding all the questions and providing volumes of information. It's an amazing award and recognizes all the hard work by our scientists over the last 10 years.

Q *Would you describe briefly your impressions from the reception at Buckingham Palace?*

A The Queen's reception was a wonderful once-in-a-lifetime experience. Many members of the royal family attended, and the atmosphere was relaxed but quite obviously regal! It was amazing to walk through the palace gates and climb the carpeted stairs to be greeted by footmen who invited us into the famous Throne Room. We waited there and talked to palace officials who then ushered us in to shake hands with and meet the Queen and the Duke of Edinburgh. We then all mingled in the picture gallery, chatting over glasses of champagne with other members of the royal family and even having a pleasant argument with the Duke of Edinburgh. I was pleased to see genuine interest in U.K. businesses. It was an amazing day.

Q *Molecular Profiles started as a spin-off from the School of Pharmacy, University of Nottingham. Molecular Profiles obviously fills an important need, what inspired you to spin off the technology from the University and how did you come to identify this niche?*

A Our research group was always interested in the importance of the physiochemical properties of materials and how this impacts pharmaceutical development. During the 1990s we were applying what were then new techniques to study these properties. The pharmaceutical industry started to ask us to look at real-time issues and problems and that's when we realized there was a commercial opportunity to be grasped.

There was also a culture of taking risks and starting companies within our School, and so we considered it a great opportunity and challenge to create something new and different in the industry. It was a step into the unknown, which made it exciting.

Q *What motivated you to co-found Molecular Profiles as a service organization rather than product development consulting?*

A Our expertise, and I suppose our passion, within the academic research group is characterization and understanding of how components function in complex systems. From that perspective a service organization fitted what we wanted to do.

Q *Molecular Profiles provides analytical services in formulation development, problem solving, and patent support. Would you please elaborate on each of the three main functions of the company?*

A In formulation development, we work with our clients to help them understand their products in development. For example we have a nanoPASS™ (predictive analytical screening solutions) service that provides a wealth of information on the physicochemical and material properties of APIs and excipients using only very small amounts of material. Under our problem solving service, we have developed a range of analytical techniques to help understand the problems down to the nanoscale level, and in our patent support services, we apply our expertise to help understand formulations in the context of patent claims and provide that evidence in a court of law.

Q *Molecular Profiles works with multiple companies, each with a specific set of needs and requirements. What have you found to be the best method for addressing each customer's set of requests?*

A Our company is about understanding systems, and this is best achieved by good communication and a collaborative approach. We can do our job best when we delve into the background of the request and get a handle on the critical issues and start working with the scientists at the company. Often we find together with our clients that the answers lay a little left of base.

Q *What information do your clients need to provide in order for Molecular Profiles to assist them with formulation development or project initiation?*

A It depends on our clients' needs. Typically we need to know what they see as the issue, their expectations, and whether they have a hypothesis. Often it is useful to understand what other analysis has been conducted. Analytical research is about drawing on all the available data to gain an understanding of the component or system.

Q *In July of 2005, Molecular Profiles relocated to new premises due to a period of sustained business growth. The new facility houses some of the most advanced pharmaceutical analysis instrumentation and technology. How have the new facilities and technology supported new business development in the last 2 years?*

A Moving to new larger premises came just at the right time. This has enabled us to recruit more scientists and to broaden our services. For example we have just expanded our materials science group and brought in a new state-of-the-art XRPD, x-ray imaging, and thermal equipment. This activity has been amazingly useful in both active characterization and drug delivery analysis.

Q *I heard that you invited Professor Robert Langer from the Massachusetts Institute of Technology (MIT) to perform the opening for the new facility and give an inaugural lecture. How long have you known him?*

A I have known Bob for many years. In fact, I first met him at the CRS Annual Meeting in Norfolk, Virginia, when I was just starting on my academic career. We have collaborated and published work together over the years; he has been a kind and supportive friend, and so I was delighted Bob accepted the invitation to open our building—he is truly a pioneer of the drug delivery field. He recently travelled to the White House to receive the National Medal of Science, a huge honour and worthy recognition of all his achievements. The pictures of him with the President are amazing.

Q *For over 6 years, as the scientific secretary of the CRS, you have observed many innovative technologies and trends for drug delivery. What is your current perspective on the field of controlled release?*

A I believe it is a very dynamic field that is continually embracing new scientific advances and developments. A greater understanding of the biological barriers and the new opportunities afforded by developments in molecular and cellular biology are providing new therapeutic targets and challenges. The promise of nanotechnology is beginning to bear fruit, with innovative delivery systems emerging. The development of smart bio-therapeutic systems, as well as bio-responsive polymeric assemblies, is a testament to the remarkable creativity of the drug delivery community. In the technology field, there are so many great examples, but I will always admire what John Patten and his colleagues achieved with getting Exubera to the market. So, it's a very exciting time for controlled release technology.

Q *On a personal note, what were the factors early on that drove you to decide to choose a career in controlled release drug delivery?*

A I don't think in my early career that I had any particular plan. I was just interested in the science and driven by the ideas and questions. I saw an opportunity in the field of drug delivery as surface properties, a big interest of mine, were important in the function of the therapeutic delivery systems. I was also lucky that I joined The School of Pharmacy at Nottingham University as a junior academic, where the drug delivery group led by Bob Davis was an exciting place to work, it was one of the leading international labs at that time. I was also fortunate that Bob was a great mentor in his own inimitable fashion, giving me little direct help but constantly questioning and encouraging me in my independent research career.

Molecular Profiles continued on page 8

Molecular Profiles continued from page 7

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

A I guess it has to be the people who have trained or worked with me who have gone on to forge strong careers in academia and industry; they have achieved so much. I suspect you know you are getting old when 16 of your students are now academics, and 5 of them have personal chairs (full professors)! I am also very proud of the success of our academic group, the Laboratory of Biophysics and Surface Analysis, that my friends and academic colleagues set up with me at Nottingham University, that in turn led to our formation of Molecular Profiles Ltd. Getting the Queens Award was amazing. I shall never forget the shock and delight of hearing the news. This is all eclipsed by my family, who are pretty special (and expensive, especially my daughter!).

Q *What advice would you give to our young graduate students as they embark on their scientific careers?*

A I would encourage them to go out and be themselves, take the opportunities that arise, be driven by the scientific questions, try to be different and not follow the crowd, enjoy their work but always have a focus on the end point, the treatment for the patient. I have a daughter who is type 1 diabetic, and I possibly pay more critical attention when reading abstracts or papers about yet another *novel* insulin delivery system in trying to assess its future therapeutic value. I know the field will produce great science and developments that will make her and many other diabetic's lives much easier in the future.

Q *Could you recommend a publication that exemplifies your work that would be particularly noteworthy for our CRS readers to read?*

A I am always excited about our latest work, and there are a number of projects I could quote. For example, our recent paper in *Advanced Materials* 19(18): 2486 (2007) is the first example of high-throughput surface analysis on a polymer array that is used to screen the best material to support stem cell growth in tissue engineering scaffolds. It arose out of a conversation with Bob Langer while visiting his labs on my sabbatical, and three years later, we finally cracked the problem. I still find it amazing we can analyze over 1,700 polymeric microdots printed on a glass slide as an array within the same time period (a matter of days) that the biological evaluation of stem cell adhesion and proliferation is assessed. As well as the Langer group, the team of people involved at Nottingham, postdoc Andrew Urquhart and postgrad Michael Taylor, together with Prof. Morgan Alexander, my academic colleague, has been amazing and great to work with. It has been, and still is, one of those great scientific projects that you just don't want to end and is already leading me into areas I would have never envisaged at the start. That's what makes science so exciting! ■

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35th Annual Meeting & Exposition of the Controlled Release Society

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Combating Counterfeit Medicines in Nigeria

Raymond T. Bartus, Ceregene Inc., U.S.A.
The Development of AAV-Neurturin (CERE-120) as a Novel Neurorestorative Therapy for Advanced Parkinson's Disease: From Concept to Clinical Trials and Beyond

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Scientifically Speaking

Temperature-Induced Protein Release from Double Emulsions for Potential Transcutaneous Immunization

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Introduction

This study is part of our effort to develop a vaccine cream that will be applied to the skin in the same way as cosmetic formulations. Skin may be a potent immunological induction site since it acts as an immune barrier by its immunocompetent cells. For a long time it was believed that the skin was impenetrable to drugs and bioactive molecules greater than 500 Da; however, vaccines that target the skin only require delivery through the outermost skin layer (stratum corneum), which is an effective but fragile barrier that can be disrupted by hydration (1). Therefore, several studies have already shown strong systemic and mucosal immune responses following topical application (2). An occlusive dressing (patch) or a semi-liquid formulation can increase skin hydration and, hence, penetration. Transcutaneous immunization has the potential to make vaccine administration easier and cheaper, while maintaining efficiency and safety, which would facilitate the implementation of worldwide mass vaccination campaigns and provide the means for a fast response to terrorist bio-attacks.

A water-in-oil-in-water ($W_1/O/W_2$) double-emulsion system consists of individual oil (O) globules that contain smaller droplets of the internal aqueous phase (W_1) and are dispersed in an external aqueous phase (W_2). Double emulsions have a compartmentalized structure that can provide a high capacity for entrapment, protection of fragile substances, combination of incompatible substances in one product, and controlled release. However, the fact that double emulsions are thermodynamically unstable presents a challenge to their practical applicability. Also, while small molecules can be transported through the oil phase in a prolonged-release profile, the delivery of proteins requires an external stimulus to trigger rupture of the globules (3). This study explores a new temperature-sensitive double emulsion that remains stable during storage and delivers the antigen upon administration to the skin.

Results for Individual Double-Emulsion Globules

Using fluorescence capillary videomicroscopy, individual $W_1/O/W_2$ double-emulsion globules loaded with fluorescently tagged bovine serum albumin (FITC-BSA) were prepared and monitored during a freeze-thaw cycle (4). n-Hexadecane phase-transition occurs around 18°C, which allows it to freeze while both aqueous phases remain liquid. Otherwise stable double-emulsion globules did not suffer instability prior to or during freezing of the oil membrane; in contrast, subsequent thawing triggered coalescence of the interior droplets with the continuous phase, termed external coalescence, which led to instant release of the encapsulated material (Figure 1).

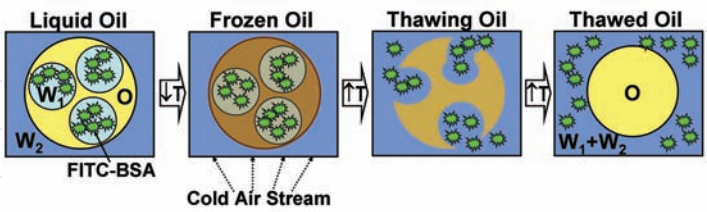

Figure 1. Scheme describing the hypothesized behavior of a $W_1/O/W_2$ double-emulsion globule loaded with FITC-BSA during a freeze-thaw cycle. Instability does not occur during freezing but during thawing of the oil phase. Reprinted with permission from Rojas and Papadopoulos (4). Copyright (2007) American Chemical Society.

Complete breakage of $W_1/O/W_2$ double-emulsion globules after a temperature cycle was proved feasible merely by tuning the size of W_1 droplets. Large W_1 droplets are inherently more unstable than their smaller counterparts, and thereby, become more susceptible to the destabilizing effects of external stimuli such as oil thawing (Figure 2). Also, varying the total volume fraction occupied by W_1 in the host globule did not affect the observed droplet-size dependence.

Results for Bulk Double Emulsions

This double-emulsion system was prepared in bulk following a two-step emulsification procedure. High-shear homogenization was first applied to obtain a stable W_1/O emulsion; then, the simple emulsion was dispersed in W_2 by gentle magnetic stirring. The composition was W_1: 2.5% (w/v) FITC-BSA in 7.4 buffer; O: 0.05 M Span 80 in n-hexadecane; W_2: 0.03 M Tween 80 in 7.4 buffer. A $W_1/O/W_2$ volume ratio of 1:1:2 was initially selected, but the stable double-emulsion globules separated as a creamy layer due to lower density (Figures 3A–D). Lowering the volume of W_2 from 50% (1:1:2) to 20% (1:1:0.5) completely prevents initial creaming (Figures 3E–H) and, thus, allows future correlation of phase separation to emulsion instability.

As illustrated in Figure 4, the emulsion stored at room temperature had already phase-separated after 1 day, while keeping it at 4°C preserved stability; this agrees with a previous study where frozen emulsions were stable for at least 3 months, even when subjected to osmotic pressure gradients (5). Subsequent thawing of the oil triggered phase separation after a

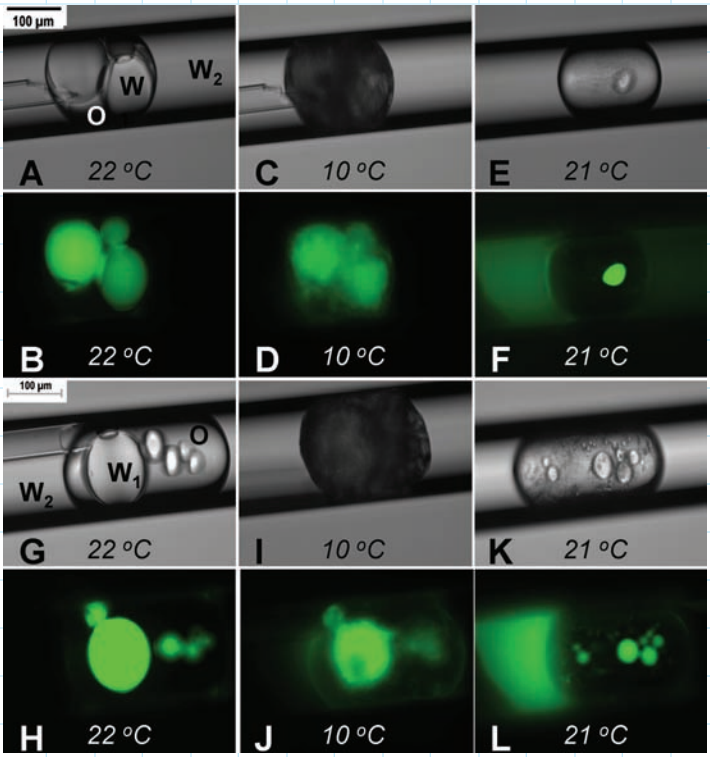

*Figure 2. Observation of stability and FITC-BSA release during the freeze-thaw cycle of two $W_1/O/W_2$ double-emulsion globules having different W_1/O volume fractions. **A** and **B**, Initial globule 1, at room temperature; **C** and **D**, crystallized globule 1; **E** and **F**, thawed globule 1; **G** and **H**, initial globule 2, at room temperature; **I** and **J**, crystallized globule 2; **K** and **L**, thawed globule 2. Panels in the first and third rows correspond to optical microscopy images, taken with bright light, whereas panels in the second and fourth rows are fluorescence microscopy images. The scale bars in panels **A** and **G** also apply to the other images. Reprinted with permission from Rojas and Papadopoulos (4). Copyright (2007) American Chemical Society.*

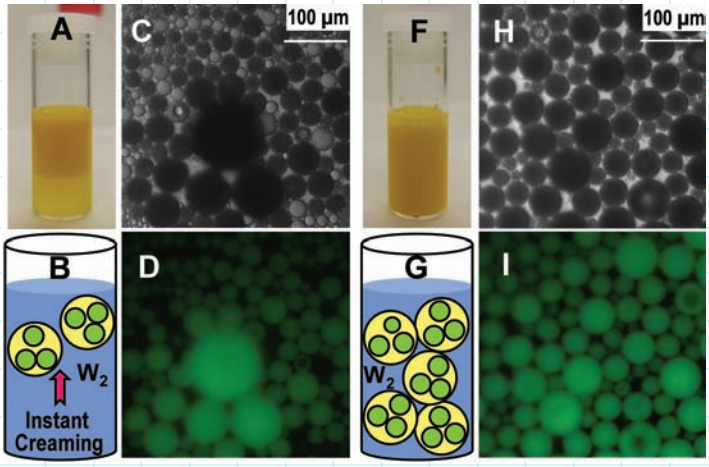

*Figure 3. Effect of $W_1/O/W_2$ volume ratio on initial phase separation of a double emulsion prepared in bulk. **A–D**, 1:1:2 ratio; **E–H**, 1:1:0.5 ratio. Panels **B** and **G** are a schematic representation of the emulsions shown in panels **A** and **F**, respectively. Panels **C** and **H** correspond to optical microscopy images, taken with bright light, whereas panels **D** and **I** are fluorescence microscopy images. The scale bars in panels **C** and **H** also applies to panels **D** and **I**.*

few minutes; however, absorbance measurements only detected 2–3% of the FITC-BSA in the bottom layer, indicating that most of W_1 was still entrapped in the creamy layer. Conducting 10 consecutive freeze-thaw cycles increased the efficiency of protein release to ≈20%.

In addition, fluorescence microscopy revealed that the top layer consisted mainly of W_1/O simple emulsion resulting from coalescence among oil globules (Figure 5). While several double-emulsion globules were still present in the control emulsion after 1 day, conducting a temperature cycle accelerated oil-oil coalescence; additional freeze-thaw cycles produced larger W_1 droplets.

Figure 6 summarizes the behavior of the studied bulk double-emulsion system when subjected to freeze-thaw cycling. Freezing the oil membrane preserved emulsion stability during storage. However, the small size of W_1 droplets (Figure 3H–I) hindered

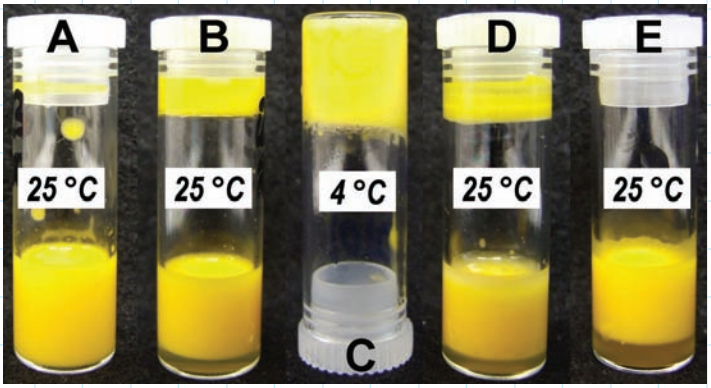

*Figure 4. Macroscopic observation of stability for the double emulsion prepared at the volume ratio 1:1:0.5. **A**, Initially; after 1 day of storage at **B**, ≈35°C and **C**, ≈4°C; and after **D**, 1 freeze-thaw cycle and **E**, 10 freeze-thaw cycles.*

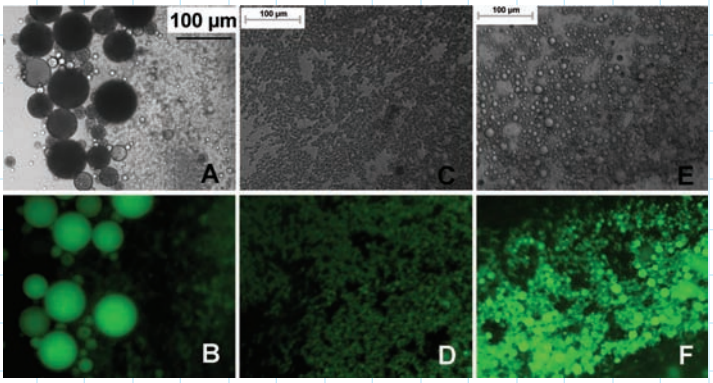

*Figure 5. Observation of instability of the creamy (top) layer of the double emulsion: **A** and **B**, Stored at ≈25°C for 1 day; **C** and **D**, subjected to 1 freeze-thaw cycle; and **E** and **F**, subjected to 10 consecutive freeze-thaw cycles. Upper panels correspond to optical microscopy images, taken with bright light, whereas lower panels are fluorescence microscopy images. The scale bar in panel **A** also applies to the other images.*

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Temperature-Induced Protein Release continued from page 11

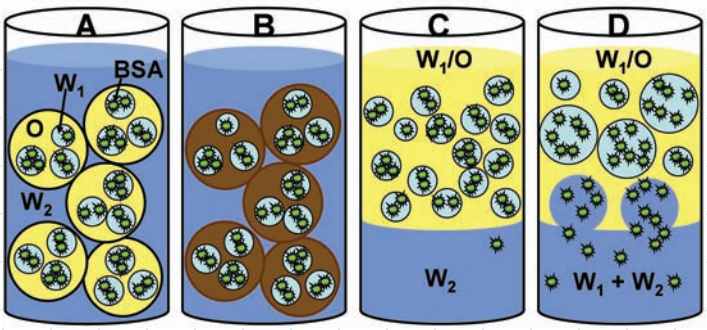

Figure 6. Scheme describing the observed behavior for the $W_1/O/W_2$ double emulsion prepared in bulk, containing FITC-BSA, during freeze-thaw cycling. ***A,*** *Initially;* ***B,*** *during storage (crystallized oil);* ***C,*** *after a freeze-thaw cycle;* ***D,*** *after several freeze-thaw cycles.*

external coalescence during oil thawing. Coalescence among oil globules further prevented FITC-BSA release by decreasing the total interfacial area and, consequently, the number of interior droplets in close proximity with the continuous phase, ultimately forming a water-in-oil emulsion that phase-separated from W_2. Several temperature cycles caused progressive growth of W_1 droplets as they coalesced with each other, eventually reaching the O/W_2 interface.

Although complete protein release after temperature cycling has not been achieved yet, our increased understanding of the phenomena will allow improvement of the delivery. For instance, we are currently exploring the hypothesis that spreading the emulsion as a thin layer will increase the interfacial area and, therefore, facilitate protein release through external coalescence.

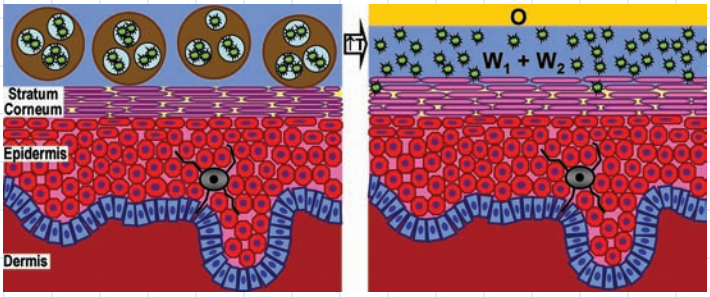

Figure 7. Scheme describing the hypothesized protein-release mechanism from the proposed double-emulsion system during administration to the skin.

Conclusions

The approach presented here has the potential to provide a stable cream-like formulation that will encapsulate and protect the antigen during storage while efficiently releasing it during administration. Macroscopically, this globule-breakage mechanism will eventually translate into complete phase separation, leaving an oil layer on top of an aqueous layer that puts the protein in direct contact with the skin (Figure 7). These layers could prevent sample loss while occluding and hydrating the skin, thus eliminating the need for a patch. The frozen oil membrane prevents mass transfer so potentially denaturating components (e.g., chemical penetration enhancers) could be stored in O and W_2, while the optimal protein microenvironment is preserved in W_1. For transcutaneous immunization, a biocompatible oil with phase transition occurring close to skin temperature (≈35°C) will eventually replace n-hexadecane.

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Scientifically Speaking

Swellable Lipid Implants: Use of Vibrational Spectroscopy to Study Lipid and Protein Structure

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Introduction

Controlled release systems have the potential to add benefit to protein pharmaco- and immuno-therapeutics because they reduce the need for multiple injections, may assist bioactives to reach target sites, and provide protection against *in vivo* protein degradation. Lipid implants constituting mixtures of lecithin (L) and cholesterol (C) are promising candidates due to their sustained release properties, efficacy, biodegradability, and biocompatibility (1,2). In mice, a study revealed rapid transformation of L:C (1:1, w/w) implants into soft, semi-solid depots after a few day of subcutaneous implantation with an anti-bovine serum albumin (BSA) response that was significantly higher than that induced by three injections of BSA solution for up to 10 months (1). The formation of myelin structures during matrix erosion was postulated to be the mechanism underlying their sustained release property (1). Hydrated lipids with different physical properties (e.g., morphology, size, surface charge, and hydration) have been reported to exhibit dissimilar *in vitro* and *in vivo* performance (3,4). Common excipients, such as salts, affect hydration/dehydration properties and phase behaviors of the L:C systems, and this may influence *in vivo* absorption and clearance. Therefore, it is essential to gain a better understanding of the effects of the excipients (salts) on *in vitro* phase behavior and protein release and physical stability.

Methods

BSA was incorporated, as a model protein, into L and L:C (1:1, w/w) matrices using a wet granulation and compression method to produce 30-mg cylindrical implants of 3 mm diameter and 3.9 ± 0.27 mm (mean ± s.d.) height. Figure 1 summarizes the *in vitro* release and analyses performed.

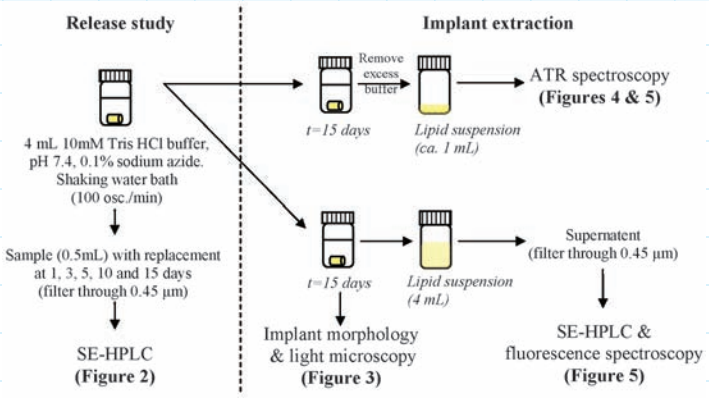

Figure 1. Schematic representation of the in vitro *release study, implant extraction, and characterization of the lipid implants.*

Results and Discussion

In the absence of salts, BSA was released from L and L:C matrices with a high monomer content, and size exclusion (SE) HPLC chromatograms were not significantly different from a BSA solution (Figure 2A). The release profiles were similar to those previously reported (Figure 2B) (2). Cholesterol significantly reduced the release, so that approximately half of the BSA released from the L implants was liberated from the

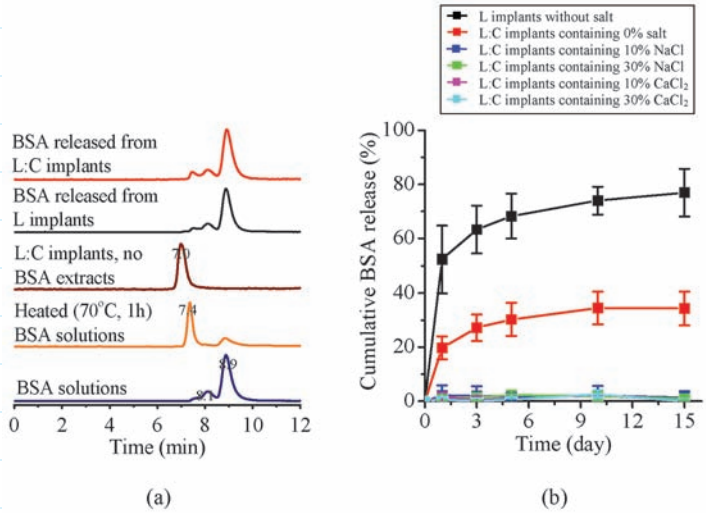

*Figure 2. Characteristics of released BSA: **A**, SE chromatograms and **B**, release kinetics from L implants without salt and L:C implants containing 0% salt, 10% NaCl, 30% NaCl, 10% $CaCl_2$, and 30% $CaCl_2$.*

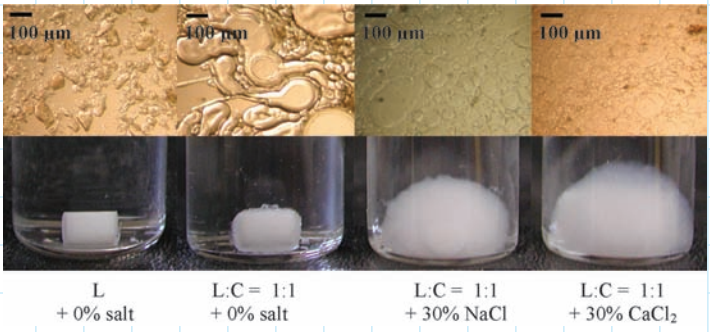

Figure 3. Morphology of the implants and their light microscopy images at 100× magnification after 15 days of incubation at 37°C.

L:C matrices after 15 days incubation. Figure 3 shows that the L implants remained unchanged without any sign of matrix erosion after incubation, whereas the L:C implants swelled. Light microscopy photographs demonstrate that particles in the L implants maintained their crystalline structures, while those in the L:C systems hydrated to form myelin structures (2). Phase transformation of the L:C matrices during incubation was evidenced by shifts of the asymmetric CH_2 stretching from 2,915 to 2,920 cm^{-1} and the asymmetric PO_2^- vibration from 1,235 to 1,222 cm^{-1} in the attenuated total reflectance (ATR) spectra (Figure 4). Salts (NaCl and $CaCl_2$) inhibited BSA release (Figure 2B) and enhanced the swelling of the L:C matrices (Figure 3). The implants hydrated into lipid vesicles of various sizes and thin membranes. The disappearance of spectral modifications due to phospholipid-Ca^{2+} interactions in the dry mixtures indicated desorption of salts from the polar headgroup upon incubation (Figure 4). Enhanced swelling of multilamellar structures of phospholipids in salt solutions has been previously noticed. Salts have a potential to strengthen lateral interactions between adjacent phospholipid molecules in the bilayers (5). Therefore, it is likely that the swollen lamellar phase induced by salts may have produced diffusional barriers resulting in retention of BSA in *in vitro* release study.

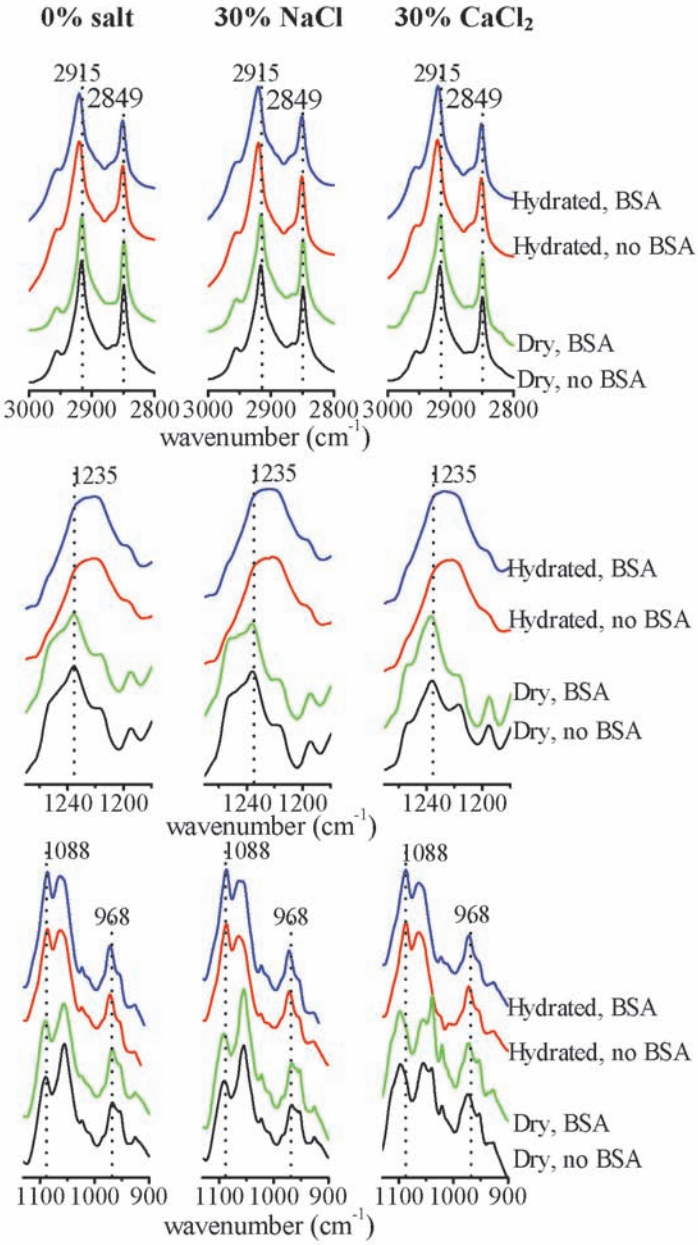

Figure 4. ATR spectra showing asymmetric CH_2 (2,915 cm^{-1}), symmetric CH_2 (2,849 cm^{-1}), asymmetric PO_2^- (1,235 cm^{-1}), symmetric PO_2^- (1,088 cm^{-1}), and asymmetric C-N-C (968 cm^{-1}) vibrations from the L:C implants.

The structure of BSA remaining in the swollen implants was investigated by SE-HPLC, fluorescence, and ATR spectroscopy (Figure 5). The chromatograms suggest that the majority of BSA maintained its monomeric form while residing in the hydrated L:C matrices (Figure 5A). The peak at 7.0 min, previously observed upon hydration of the blank L:C implant, supported the light microscopy images of hydrated lipid vesicles (Figure 3). The peak at 7.4 min designated BSA aggregates as the peak position coincided with soluble aggregates found following thermal treatment (70°C, 1 h) of BSA solution. Blue-shifts in the maximum wavelength of the intrinsic fluorescence emission spectra from 343.0 ± 1.4 nm (BSA solution) to 341.7 ± 1.5, 342.0 ± 1.0, and 338.7 ± 0.6 nm when the L:C matrices comprising 0% salt, 30% NaCl, and 30% $CaCl_2$, respectively, confirmed the perturbation in the BSA structure, possibly via aggregation or binding of BSA onto the hydrated lipid vesicles. Increased intensity of the peak at 1,234 cm^{-1} in the L:C + 30% $CaCl_2$ implant suggests replacement of water upon binding of BSA onto hydrated lipids and can be used to indicate the importance of protein adsorption as a mechanism underlying the retention of BSA (Figure 4). The ATR spectra, decreased intensity, band broadening, and shift of the α-helix peak toward lower wavenumber indicated some rearrangement of the BSA structure upon incubation (Figure 5B). However, the peaks (1,618 and 1,692 cm^{-1}) corresponding to aggregation were not presented in any of these spectra. For the L:C + 30% $CaCl_2$ implant, the ATR spectrum did not reflect increased amount of BSA aggregates as illustrated by the chromatogram (Figure 5). This may indicate the association of BSA to form multimers with high retention in its secondary structure and/or it is possible that structural alterations induced by salts did not take place via intermolecular β sheet structure, which is dissimilar to the mechanism stimulated by thermal denaturation.

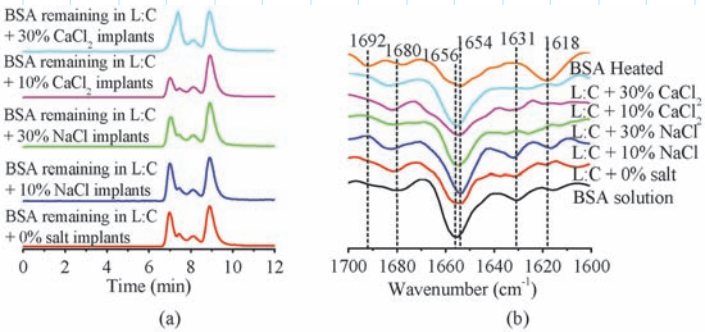

*Figure 5. Structural analysis of the BSA retained within the swollen L:C implants from **A**, SE-HPLC and **B**, ATR spectroscopy after incubation. The ATR spectra in the amide I region were preprocessed by second derivative calculation with 9 points smoothing, baseline-corrected, and area normalized to unity.*

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Swellable Lipid Implants continued from page 15

Conclusions

This work demonstrated the potential of salts in enhanced swelling, inducing the formation of lipid aggregates of different morphology and inhibiting the *in vitro* release of BSA from the L:C implants. The formation of the swollen lamellar phase surrounding the L:C implants may result in diffusional barriers that delay BSA release. This effect was strengthened by increased adsorption of BSA onto hydrated lipid vesicles. While residing in the swollen matrices, the majority of BSA maintained its monomeric form, with a slight increase in the amount of soluble aggregates. Some secondary structure perturbation occurred without any sign of aggregation. These results suggest the possibility of BSA association to form multimers with high retention in the native secondary structures and/or salt-induced BSA denaturation in a pathway dissimilar from that stimulated by thermal denaturation.

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Optimizing Transdermal Drug Delivery Through Diffusion Modeling

By Adam Powell, Ph.D.
Veryst Engineering, U.S.A.

Transdermal patches are an increasingly popular mode of drug delivery. A drug is mixed into an adhesive polymer or gel with a diffusion enhancer if necessary and cast into a patch, which is applied to the skin. Because patch thickness in this drug-in-adhesive design is much smaller than its width, drug transport out of it is inherently one-dimensional. Skin is somewhat more complex (Figure 1), though the stratum corneum layer of dead epidermal cells usually controls drug transport. The cells' aspect ratio and number of cell layers (typically 10–20) make one-dimensional (1-D) continuum diffusion a reasonable approximation of transport across the skin.

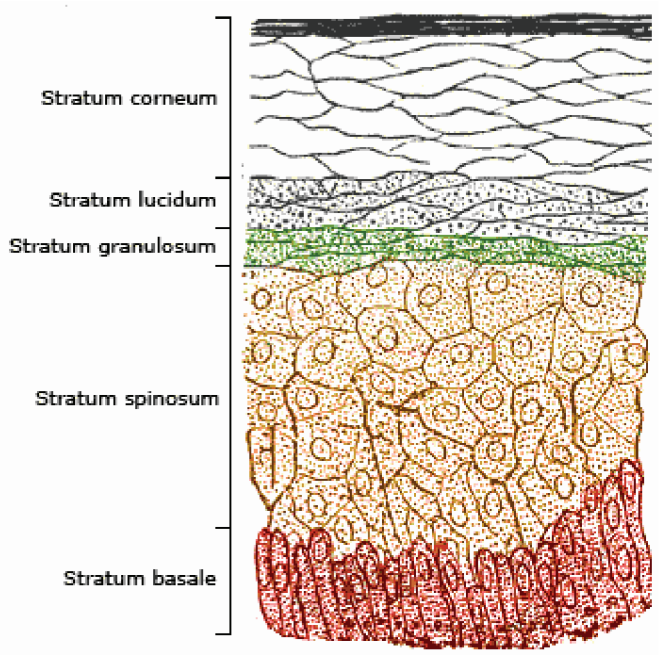


Figure 1. Schematic illustration of epidermis layers.

Patch designers must tune various parameters, such as thickness, area, adhesive formulation, and drug and enhancer concentrations, to meet several objectives, including drug dosage-time profile, avoiding irritation, and small dimensions for reduced cost and good user experience. Experiments using various combinations of parameters involve expensive clinical trials with potentially long evaluation periods. Models that predict the delivery kinetics of transdermal patches accelerate this process, by enabling

- Rapid optimization of transdermal drug delivery parameters
- Insight into factors governing optimal delivery
- Reduction of number and duration of clinical experiments
- Archiving knowledge for rapid development and employee education

We, therefore, present here a user-friendly cross-platform spreadsheet implementation of a 1-D diffusion model of transdermal delivery that estimates drug delivery profile and concentration as a function of position and time. This model provides all of the predictive capability of other 1-D models, e.g., those of Rim et al. (4), but works across operating systems without requiring complex and expensive software.

1-D Transient Finite Volume Model

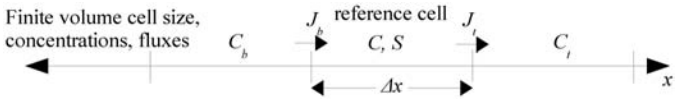
The spreadsheet provides a one-dimensional finite volume (FV) diffusion model. This method is a close cousin to finite difference (FD) and linear finite element methods (FEM); for a homogeneous material in one dimension, the three methods produce the same equations, though FV and FEM facilitate setting exterior and interior boundary conditions. The FV method divides the patch and skin into layers, called "cells," of finite thickness (Δx), and solves the conservation equation below for each cell:

$$\Delta x \frac{\partial C}{\partial t} = J_b - J_t + \Delta x S,$$

where C and S are the drug concentration and generation rate in the cell ("generation" here refers to chemical reaction that adds or removes the chemical, e.g., metabolism in living skin cells), and J_b and J_t denote fluxes on its bottom and top surfaces, as shown in the figure below. The fluxes are in turn given by Fick's law:

$$J = -D\frac{\partial C}{\partial x} \approx -D\frac{\Delta C}{\Delta x},$$

where D is drug diffusivity. The model, thus, requires eight parameters, four each for the skin and patch layer, which are thickness, diffusivity, initial concentration, and number of FV cells in that layer.



In this example, we use explicit (a.k.a., forward Euler) timestepping to solve the governing equations. Although much simpler than implicit methods, explicit timestepping limits the size of time steps for numerical stability. This can require large numbers of time steps to simulate the useful lifetime of a patch.

The spreadsheet stores concentration values in a grid, where position (x) is measured from left to right and time (t) downward from the top. A given concentration (C_{new}) depends

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on the concentrations in that cell and its neighbors in the previous time step, i.e., the previous row: C_{old}, C_b, C_t. This simple model assumes zero flux at the top of the patch and zero concentration at the bottom of the skin layer. These are typical assumptions for transdermal drug delivery modeling.

Example

Consider the example of a small molecule drug with constant diffusivity moving from a thin patch into the skin. A first simulation might correspond to a patch with a weak enhancer or no enhancer. Figure 2 shows the front-end sheet of the spreadsheet implementation of this model. This includes a graph showing drug delivery per unit area as a function of time, and one showing drug concentration distribution through the skin and patch at several times, along with editable model parameters highlighted in orange. The maximum flux calculated by this simulation is very small, and the drug concentration in the patch rises relatively slowly, taking an hour to reach its maximum dosage level. The 4,000-timestep numerical finite volume solution refreshes in less than a second on modern hardware.

Well-known analytical solutions demonstrate the validity of this numerical model. In the short term, an error function solution to the diffusion equation provides a good estimate for the concentration in the skin, giving a square root-exponential relationship between flux and time (Kalia and Guy [1], eq. 19). In the long-term case with diffusion through skin limiting transfer of the drug, its concentration falls uniformly in the patch according to the flux through the skin (Kalia and Guy [1], eq. 20). As shown in Figure 2, the numerical finite volume solution is similar to short- and long-term analytical solutions.

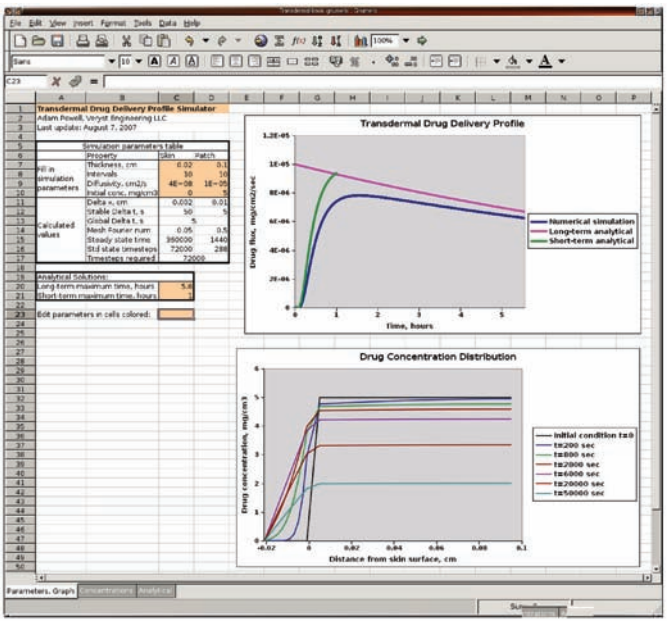

Figure 2. Spreadsheet model of transdermal drug delivery, with details of 4,000-timestep finite volume simulation and analytical solutions in separate sheets.

If this dosage is not sufficient, or takes too long to establish (e.g., for pain medication), there are several potential approaches to improving patch performance. One is to add a diffusion enhancer, which increases the diffusivity of the drug in the skin. Figure 3 shows the effect of increasing the diffusivity in the stratum corneum by a factor of 10: the drug concentration quickly establishes a linear profile across the skin, and diffusion through the skin limits its transport. As shown in Figure 4, this results in a much quicker rise to a much higher maximum flux followed by faster quasi-steady depletion of the drug from the patch. The timescale of rising and falling concentrations, and the maximum flux, all change by a factor of 10, as predicted also by the short- and long-term analytical solutions.

The model thus far, while illustrative, does not do significantly more than one can with analytical equations. But its power lies in its flexibility, e.g., its ability to manage complex initial conditions or multi-layer patches. Figures 5 and 6 show the concentration distribution and flux profile for a two-layer patch. Here, a thick top layer supplies most of the drug over the long term, and a thin base layer boosts the flux when first applied. This two-layer patch, thus, achieves a more uniform profile over time than would be possible with a single-layer drug-in-adhesive passive patch. Contrast this drug delivery profile with Figures 2 and 4 and the adjusted analytical solutions for the main drug layer, illustrating the ability to tailor the history of drug delivery through patch design. Though it took many iterations of adjustments to reach

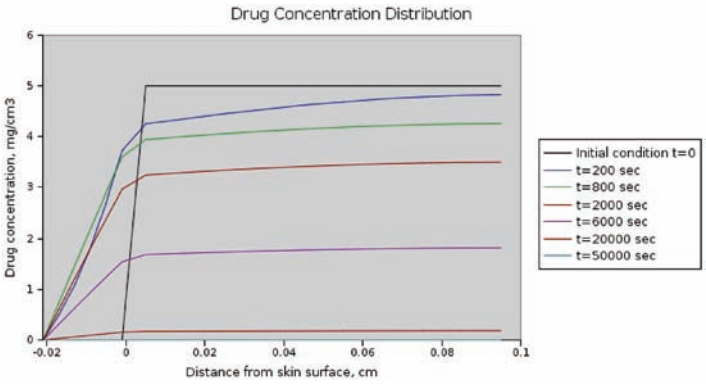

Figure 3. Calculated concentrations in skin and patch with large skin diffusivity.

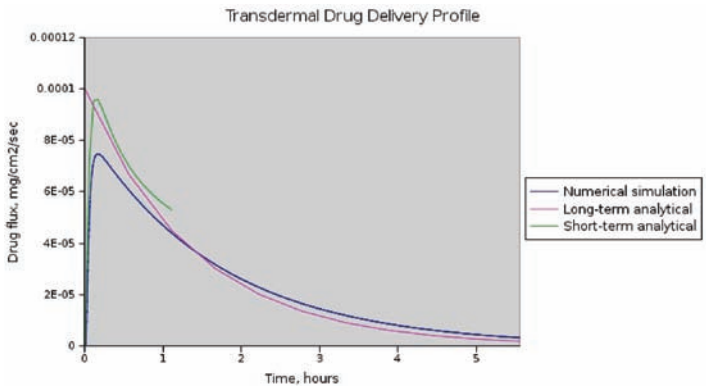

Figure 4. Calculated drug flux at base of stratum corneum with large skin diffusivity.

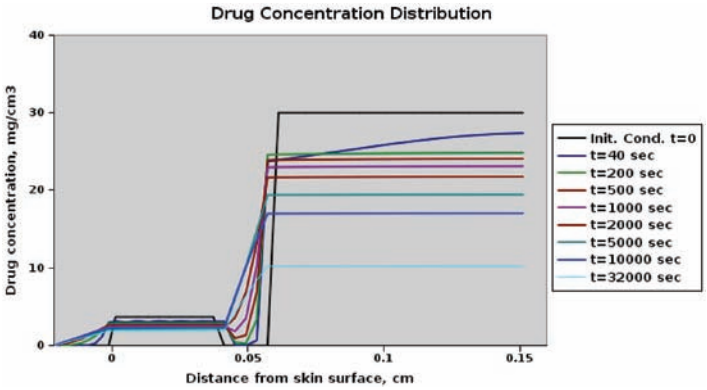

Figure 5. Calculated concentrations in skin, base layer, membrane, and top layer of a multilayer patch.

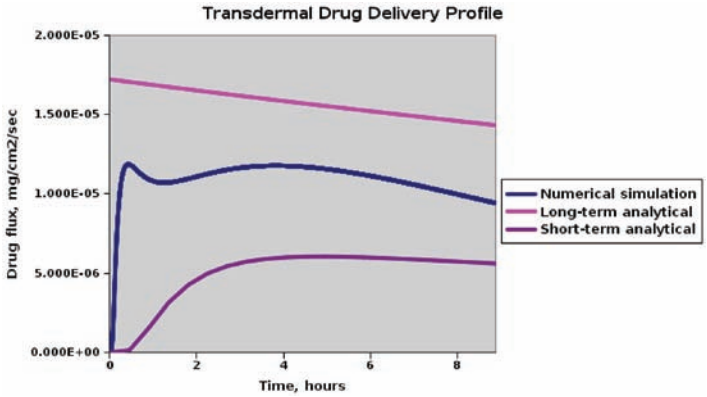

Figure 6. Calculated drug dosage profile over time of a multilayer patch, with two illustrative analytical solutions.

the set of parameters that produce this uniform profile, those model iterations are vastly less expensive than multiple experiments to achieve the same end.

This multi-layer patch simulation, with a much lower diffusivity in the membrane layer, requires considerably smaller timesteps, and thus many more timesteps, to simulate the same amount of time. Nonetheless, the simulation with 30,000 timesteps and a total of 33 cells across its four layers (cf. 20 for the basic patch simulations) refreshes in about 10 seconds on modern hardware, though it requires about half a gigabyte of RAM to do so.

More Complex Capabilities

This illustrative model assumes identical drug solubility in the patch and skin and constant uniform drug diffusivity in the skin. One can correct the former by incorporating a partition coefficient at the skin-patch interface. Correcting the latter requires coupling with a model of enhancer diffusion, and making each diffusivity a function of both concentrations. This would double the number of variables, obviously increasing the refresh time; the use of a function for the diffusivity will increase the refresh time further. Diffusivities can also depend on location or other environmental influences such as temperature and humidity, and the model can incorporate these effects by varying diffusivity with position and/or time.

Adding electrical phenomena such as iontophoresis is straightforward, as long as one can assume ion diffusion through the skin is one-dimensional. (There is evidence suggesting that iontophoretic delivery takes place primarily through hydrophilic pores, which would complicate diffusion; e.g., Lai and Roberts [3]). A diffusion analogue to the enthalpy method for modeling heat transfer with phase change can model coupled drug dissolution along a front and diffusion through the patch. If the drug crystallizes in the polymer adhesive, crystal dissolution kinetics, such as in the model of Kurnik and Potts (2), would be less straightforward to add. But, if the crystals are small and their size and density distribution is known, it should be possible to include this as well while retaining the spreadsheet's simplicity.

It is worth noting that the multi-layer patch simulation described above, with its strongly different diffusivities and cell thicknesses in the different layers, requires more computational work, and thus longer refresh time, than any of the other proposed changes mentioned here.

Summary

We believe that modeling the kinetics of drug diffusion in transdermal patches can be of enormous value. The simple model and examples presented here demonstrate how simulations can both assist fundamental understanding and guide experimental and clinical efforts.

This model provides most of the features of numerical simulations written in compiled languages such as C or FORTRAN. The spreadsheet is considerably easier to distribute and use, as spreadsheet software is ubiquitous and skilled users are abundant. It is straightforward to enhance the model to simulate more complex phenomena, such as electromigration or coupling with enhancer transport. Though it runs more slowly than compiled code, the model's simplicity leads to a short refresh time, making this a useful tool for the design of transdermal patches.

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SPOTLIGHT:

Delcath Systems, Inc.

By Jason Rifkin
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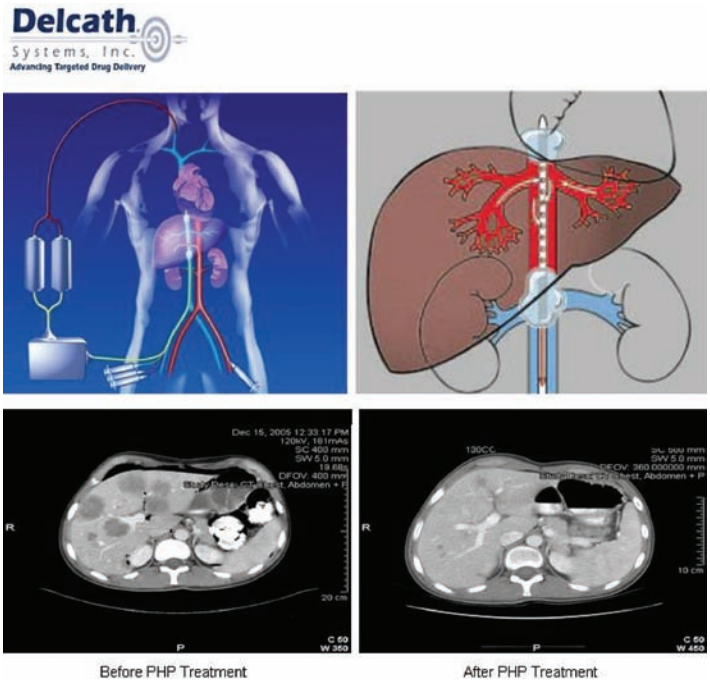
Delcath Systems is a medical technology company testing a drug delivery platform for the targeted delivery of ultra-high doses of chemotherapeutic drugs while protecting patients from the harmful side effects of chemotherapy. Doctors at the National Cancer Institute (NCI) use catheters placed percutaneously in a process called percutaneous hepatic perfusion or PHP. Having produced dramatic responses in Phase I clinical trials, the testing leaped to the pivotal Phase III trial, which is currently underway.

The Delcath System is currently being used to treat a variety of tumors in the liver but can be adapted to isolate other organs and body regions, as demonstrated in animal trials. By isolating an organ, the Delcath System allows for the targeted delivery of chemotherapeutic agents in much higher doses, thereby improving therapeutic benefit while minimizing systemic toxicity. The Phase III trial currently underway at the NCI is delivering several times the FDA approved dosage of melphalan for the treatment of metastatic melanoma in the liver. The NCI is also currently enrolling patients in a Phase II trial of the Delcath System for primary liver cancer and metastatic hepatic malignancies from neuroendocrine cancers and adenocarcinomas, as well as for patients with melanoma who are not eligible for the phase III trial.

The Delcath System
Because most unresectable tumors in the liver are rapidly fatal (expected survival is less than a year), the first application of Delcath's technology is for the treatment of various cancers in the liver. The Delcath System allows for the delivery of high doses of chemotherapy to the liver with subsequent filter-based removal of the drug from the blood prior to its return to the patient's general circulatory system. This filtration protects the rest of the body from the harmful side-effects of chemotherapy, which allows for much higher doses of drug to be administered to the tumors in the liver; those higher doses have shown promising tumor responses. The Delcath System is minimally invasive and repeatable. The versatility of the technology gives it the potential to be used with different therapeutic and chemotherapeutic agents and for the isolated treatment of cancers in the limbs, kidneys, and pancreas, among other locations. The company is currently evaluating use of the Delcath System with various agents for the treatment of hepatitis, a disease of the liver that affects millions worldwide.

The crux of the Delcath System is a 16-F double balloon catheter with one large lumen and three accessory lumina. This catheter is inserted into the inferior vena cava, where it isolates the hepatic venous outflow and allows for high-dose infusion of chemotherapy directly to the liver. The two occlusion balloons are inflated independently through separate lumina. The cephalic balloon blocks the inferior vena cava above the hepatic veins, while the caudal balloon obstructs the inferior vena cava below the hepatic veins, allowing for complete isolation of hepatic venous outflow. Between the balloons is a fenestrated segment that feeds into the large central lumen that exits the catheter from the proximal end. Contrast medium is injected in a retrograde fashion through the fenestrated portion of the catheter to ensure that the balloon catheter is properly placed and the hepatic venous outflow is isolated without leakage into the right atrium. There is an additional lumen that allows some blood flow from the inferior vena cava below the liver to the right atrium. During the procedure, a very high dose of melphalan is infused for 30 minutes through a catheter percutaneously inserted into the artery. This hepatic arterial catheter is positioned in the proper hepatic artery using standard fluoroscopic and arteriographic techniques. The melphalan



Top left: Diagram depicting the Delcath System. The drug is infused through the catheter in the artery (red), is trapped between the balloons in the liver, and flows out to be filtered before the cleansed blood returns to the neck. Top right: An enlargement shows the balloons blocking normal flow, so the blood travels downward through the catheter to be filtered outside the body. Bottom left: A scan of a liver before treatment using the Delcath System. Bottom right: A scan of the same liver after one Delcath treatment.

perfuses the liver and exits the organ through the hepatic veins. Hepatic venous effluent is collected using the occlusion balloon catheter, and melphalan-dosed blood from the central lumen is pumped through an extracorporeal circuit consisting of a centrifugal pump and two hemoperfusion drug filtration cartridges. The filtered blood is returned to systemic circulation via a venous return sheath inserted into the internal jugular vein. The isolation and filtration continues for an additional 30 minutes following infusion, preventing the drug being reintroduced into systemic circulation from the saturated liver. At the end of the procedure, the catheters are removed and compression is applied to the catheter insertion sites. After the procedure, the patient is kept on bed rest and is monitored in the intensive care unit for 12 hours. The diagram depicts the Delcath System.

Company Background and History

Delcath Systems became a public company in 2000 and is listed on NASDAQ under the ticker symbol DCTH. The company has a new management team and a new Board of Directors, composed of leaders in oncology, industry, and finance. The company also has medical thought leaders in the fields of interventional radiology and oncology as scientific advisors. The technology behind the Delcath System originated with three physicians at Yale and has been perfected through several hundred treatments. With the foundation laid, Delcath is focused on obtaining FDA approval for the Delcath System as early as 2009.

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Fish Oil Microencapsulates for Food Products

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Introduction

Nowadays more and more studies suggest that polyunsaturated fatty acids may lower the risk of cardiovascular disease and some forms of cancer and may play a key role in brain development (5,9). Omega-3 fatty acids such as α-linoleic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are of special interest (Figure 1). The polyunsaturated fatty acids are essential to human health but cannot be made in the human body. They can be obtained from eating fish that feed on microalgae. However, the average amount of omega-3 fatty acids in a Western style diet is about 0.15 g per day, far lower than the recommended dose of 0.4–1.0 g (5,9). Therefore, fortification of food products with fish oil is an elegant way to provide humans with omega-3 fatty acids and, thus, has become one of the most prominent and fastest growing trends in the food health sector. Unfortunately, polyunsaturated fatty acids are very unstable and are prone to oxidation, leading to the development of rancid, fishy off-flavours due to formation of aldehydes, alkanes, and ketones with time. Oxidation of fish oil might be prevented by exclusion of oxygen, light, and metal ions (especially iron and copper), operating at low temperatures, and/or use of antioxidants and metal scavengers. Proper handling of the raw materials together with optimum design of the food microstructure and composition are possible routes for reducing oxidation. This paper will focus on microencapsulation for improving the stability of omega-3 fatty acids and subsequently promoting their utilization in various food systems. Many microencapsulated fish oils or other polyunsaturated fatty acids have been developed and have been on the market for quite some time. They all claim enhanced protection against oxidation and easy handling.

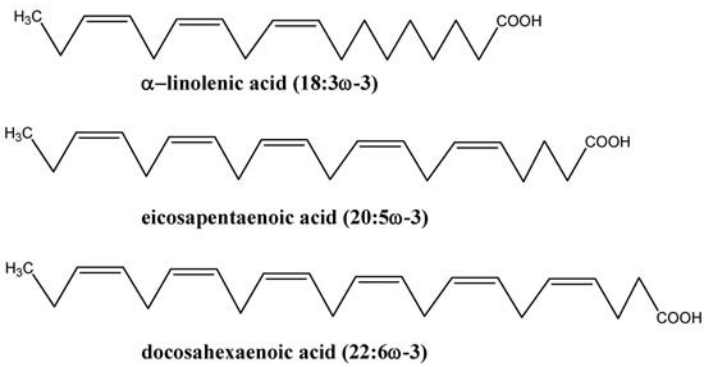

Figure 1. Chemical structures of the omega-3 fatty acids ALA, EPA, and DHA.

Requirements and General Characteristics of Fish Oil Microencapsulates

Microencapsulation broadens the scope of application of sensitive fish oil in diverse food applications (orange juice, bars, cereals, etc.)—a result of the oil's enhanced stability. In theory, microencapsulation of fish oil can prevent off-flavour development by

- Preventing contact between oxygen and the omega-3 fatty acids
- Preventing contact between metal ions and the omega-3 fatty acids
- Preventing direct exposure to light
- Trapping off-flavour

Most of these benefits can be realized by entrapping the fish oil in a glassy state, since below the glassy state molecules in amorphous materials have little relative mobility. Within glassy encapsulates, it is possible to entrap pressured gas or aroma, so this may indicate that exclusion of oxygen and entrapment of volatile off-flavours might be possible by encapsulating fish oil in a glassy state material. Another advantage of microencapsulation is the possibility of converting the liquid oil substrate into a powder, thus providing ease of handling during transportation and further incorporation into food systems.

Some fish oil microencapsulates may dissolve in water and, therefore, will not be stable in aqueous food products. Water-insolubility of microencapsulates, therefore, may be an important requirement, but care has to be taken to prevent sandiness and consumer notice. Finally, the fish oil from microencapsulates should be bioavailable upon consumption and, if intact upon storage in a food product, should disintegrate in the gastro-intestinal tract.

Techniques to Produce Microencapsulates

Table 1 provides an overview of various technologies commonly applied to microencapsulated fish oil. These technologies are briefly described below, and the interested reader is referred to the references for more details.

- Spray-drying is one of the oldest routes for encapsulating oils and flavours. It is performed by spraying an oil-in-water emulsion containing carrier material dissolved in the water phase into a chamber with a flow of hot air. The water is then evaporated. A variety of carrier materials can

be used, such as maltodextrin, proteins, sugars, gums, and/or modified starch (1,4,7,8).
- Melt injection is based on pressing a molten mixture of starch (maltodextrin), fish oil, additives (e.g., antioxidants, sugars, emulsifiers), and water through a filter at a temperature above 100°C into a cold organic solvent (usually iso-propanol). The cold solvent solidifies the extrudates, which are further washed with a terpene (e.g., with limonene) to remove surface oil (13).
- Submerged co-extrusion is based on simultaneously dropping of an oil droplet and shell material through a concentric nozzle in a stream of cooling oil. The shell material typically consists of gelatine and glycerol. This process results in microcapsules with very high yields, in the neighbourhood of 90%, wt% (12).
- Complex coacervates are made from an oil-in-water emulsion in which droplets of polymer-rich phase precipitate on the interface of oil droplets, thereby forming a shell. The most famous example is with gelatine and gum arabic, which are dissolved in the water phase and then precipitate on the emulsion surfaces by adjusting the pH from neutral to about 4 under turbulent conditions at >35°C (above the gelation temperature of gelatine). The system is then cooled to about 4°C to gel the gelatine. Alternatively, other cationic or anionic biopolymers can be used, such as whey proteins or carboxymethylcellulose. Optionally, the gelatine biopolymer can be enzymatically or chemically cross-linked to make the coacervates more robust. Fish oil complex coacervates composed of gelatine or β-lactoglobulin, gum arabic, and starch, crosslinked with glutaraldehyde, have been reported to be less sensitive to oxidation (10).
- Microspheres with fish oil can be made instantaneously by dropping an alginate solution (1.5–4%, wt%) with fish oil droplets into a calcium chloride solution (50–100 mM). Alternatively, microspheres can be prepared via water-in-oil emulsion routes. Most likely, the porous calcium alginate network formed cannot reduce oxidation by preventing diffusion of oxygen or metal ions to the oil. Only a few studies exist that claim additional coating with hydropropyl cellulose (2) or xanthan gum, for example, followed by a hardening step (3).
- Calcium carbonate capsules can be prepared based on electrostatic deposition of small calcium carbonate particles on the surfaces of negatively charged oil-in-water emulsions (11). The calcium carbonate will dissolve at the low pH of the stomach.
- Emulsions of fish oil-in-water can be multilayered with biopolymers using a layer-by-layer technique (6). First, an emulsion is made with a negatively charged surfactant, followed by incubation with the positively charged chitosan and then a negatively charged biopolymer such as pectin. In theory, this sequence of incubations can be repeated until a desired layer thickness is achieved. Unfortunately, most of the (limited) studies have been done using chitosan, and this polymer is currently not food grade in the United States and the European Union.

In general, the presence of moisture may decrease the glassy state transition temperature and, therefore, increase molecular mobility in the microcapsules, thus exposing the oil to oxidation. The use of antioxidants (especially lipophilic ones such as tocopherols), shielding from light, and packaging of the fish oil microencapsulates under nitrogen or vacuum in metallised packaging material might enhance their shelf stability.

Selection Criteria for Application in Food Products

Currently both fish oil and fish oil encapsulates are widely used in food applications (bread, orange juice, cereals, bars, etc.). One can assume that encapsulated fish oil is more expensive than native fish oil, so microencapsulated fish oil should only be used when an acceptable end product cannot be made with native fish oil. To select an appropriate fish oil microencapsulate, the following criteria might be relevant:

- Quality of fish oil to apply (including the absence of off-flavours and high EPA and DHA content)
- Physico-chemical characteristics of the microencapsulates
- Stability during processing and storage in a food product (which may depend on the composition of the food matrix and packaging)
- Desired payload
- Cost
- Legal status (e.g., the use of cross-linking agents)
- Possible halal or kosher status (e.g., use of pig gelatine or chitosan might be an issue here)

Much depends on the application. One may choose a microencapsulated fish oil to facilitate transportation, handling, and processing. The structure of the food matrix is also important; for example, water-soluble microencapsulations will dissolve rapidly in aqueous food products and, therefore, cannot provide any further protection. The presence of different macro- and micro-nutrients in the food product may also influence the

Table 1. *Characteristics of commonly used fish oil microencapsulates.*

Technology	Load (wt% of dry weight)	Particle Size (µm)	Water-Soluble?	Expected Price Range
Spray-drying	1–60	10–400	Yes	Low
Melt injection	10–20	200–2,000	Yes	Middle
Submerged co-extrusion	70–95	1,000–5,000	Yes	High
Complex coacervates	40–90	10–800	No	Middle
Microspheres	20–50	10–800	No	Middle
Calcium carbonate capsules	25–40	20	Only at low pH	High
Layer-by-layer	70–90	0.2–10	No	Middle?[a]

[a]Not commercially available.

Fish Oil Microencapsulates continued on page 24

Fish Oil Microencapsulates continued from page 23

oxidative stability of fish oil, e.g., vitamin C (L-ascorbic acid) may act as either an antioxidant or a pro-oxidant.

Future research might be aimed at improving existing technologies, developing new ones, making water-insoluble microencapsulates with fish oil that are storage stable and do not sediment in an aqueous food product, and providing further evidence for prevention of oxidation and off-flavour in real food products while keeping the fish oil fully bioavailable.

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Chapter News

Israeli Chapter of the Controlled Release Society Annual Meeting Held in Caesarea

The 2007 Annual Meeting of the ICRS, held in September in Caesarea, was a very successful event with more that 250 participants. The general topic of the conference was "Advances in Drug Delivery—New Carriers, Devices and Therapies." The scientific program (www.icrs.org.il) included 2 keynote speeches and 26 invited lectures in 6 sessions, presenting anti-cancer therapies, nanotechnology in pharmaceutical design and diagnostics, CNS targeting, delivery of poorly absorbed drugs, and drug delivery devices, as well as IP and regulatory issues. There were 97 participants from industry, 56 from academic staff, and 92 graduate students who received subsidized registration. Two students were selected by the Organizing Committee to present their research results as lectures during the meeting. A rich and full poster session (71 presentations) highlighted exciting and innovative research in the field of drug delivery for the conference attendees.

Prof. Elka Touitou, President ICRS, opened the conference, presenting the CRS mission and activities, as well as detailed statistics and activities of the local ICRS chapter. CRS is the leading multidisciplinary society dedicated to the science and technology of controlled release and delivery of drugs and biomaterials. Prof. Touitou emphasized the ICRS functions and its contributions to CRS activities. She welcomed the participants, acknowledged the efforts of the Organizing Committee, and thanked the CRS and 15 other sponsors of the meeting.

The first keynote presentation was by Prof. Elias Fattal (University of Paris-XI) on "Biodegradable Particles for the Intraocular Delivery of Nucleic Acids." The second day's keynote speech was by Dr. Ron Tomer (VP Unipharm) on "How Can 'Inventions' Destroy Innovation." Two additional guest lecturers were Prof. Tamara Minko (Ernest Marion School of Pharmacy, Rutgers, NJ) and Dr. Zvi Ladin (Boston MedTech Advisors).

The first day of the conference culminated in a Gala Dinner in the picturesque Hazer haBeer garden. At this pleasant event, the participants enjoyed a romantic, country atmosphere, tasteful cuisine, and fun-filled dancing. During the Gala Dinner, Prof. Roza Azhari, ICRS President Elect, presented previous ICRS meeting awards for the most outstanding student presentations to five students. These awards encourage student participation at the international CRS meetings.

The 2007 Prize Committee, composed of five members from industry and academia, selected the winners of the traditional ICRS student poster competition: Tomer Bronshtein (Technion), Oded Ovadia (Hebrew University of Jerusalem), Margarita Shumilov (Hebrew University of Jerusalem), Avi Schroeder (Ben-Gurion University), and Ehud Segal (Tel-Aviv University). Also this year, a new ICRS Award for Achievements in Drug Delivery was given to Prof. Michael Friedman (School of Pharmacy, The Hebrew University of Jerusalem).

Israel is a country with dynamic and creative research in the field of drug delivery and nanomedicine. This ICRS meeting enabled scientists from academia and industry to meet and exchange ideas, thus encouraging and promoting ongoing and new research in the field of drug delivery. ■

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Mark E. Davis
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Nanoparticle Cancer Therapeutics: From Concept to Clinic

Jackie Y. Ying
Agency for Science, Technology and Research, Singapore
Nanostructure Processing of Advanced Biomaterials and Biosystems

Submission closes on January 31, 2008, so beat the rush and get your abstracts and nominations in before the end of 2007. You'll be glad you did.

At the 35th CRS Annual Meeting & Exposition in New York, you'll experience the diverse programming, high-quality science, and in-depth discussions that you've come to expect from CRS. Mark your calendar now for next summer's hot event in the Big Apple! Visit the CRS website often for Annual Meeting & Exposition news. Watch the Exhibitor list for the companies you need to meet with. Remember, the shopping in New York is the best in the world.

See you there! ■

What's on Board

Committees Vital to Success of CRS

At the September CRS Board meeting, the Board of Directors spent hours discussing committees and how vital they are to the success of the CRS. It didn't take long for all involved to clearly see that CRS is an active, smooth-running society because of member volunteers. Thanks to all of you!

There are many opportunities within CRS to share your ideas and expertise, so consider volunteering today. It's not too late to sign up to review abstracts or help create new ways to add member value and increase awareness of CRS around the world.

To help you decide which committee to join, who to contact, and what is available, here's some helpful information:

Abstract Reviewer

Task: Assist in securing annual meeting reviewers and serve as reviewer.
Contact:
Ijeoma Uchegbu
Ronda Thompson

Chapter Committee

Charge: Increase interaction between Local and Student Chapters and CRS membership.
Chair: Mahesh Chaubal
Ex officio:
Elka Touitou
Ronda Thompson

Consumer and Diversified Products Committee

Charge: Increase awareness of CRS outside of the C&DP Committee and keep CRS membership informed about those involved in C&DP who are leaders in their fields of delivery and use of bioactives.
Chair: Chuck Frey
Members:
Chris Barbe
Todd Becker
Manmohan Bhakoo
Michael Calandra
Doug Dale
Nava Dayan
Anil Gaonkar
Mark Gebert
Harlan Hall
Linggen Kong
Jamileh Lakkis
Kelly Miller
Toshiro Ohtsubo
Claudio Ortiz
James Paik
Paul Richardson
Meyer Rosen
Birgit Schleifenbaum
Ruth Schmid
Sam Shefer
Chris Soper
Niraj Vasisht
Ron Versic
Teresa Virgallito
Gulden Yilmaz
Qin-Qiu Zhao
Ex officio:
Elka Touitou
Ronda Thompson

Education Committee

Charge: Conduct four webinars in 2007–2008, expand the mentorship program, and continue the successful Young Scientist events at the annual meetings.
Chair: Farid Dorkoosh
Members:
Ronnie Ortiz
Siddhesh Patil
Mike Rathbone
Dody Reimer
Sevda Senel
Avi Thombre
Ron Versic
Rod Walker
Haiyan Zhang
Ex officio:
Lisbeth Illum
Ronda Thompson

Marketing Committee

Charge: Assist in creating and implementing a marketing plan to increase attendance at the New York Annual Meeting & Exposition.
Chair: Claire Madden-Smith
Members:
Vinay Chhatre
Doug Dale
Joe Fix
Ken Hinds
Bill Jones
Chris McDaniel
Nigel Ray
Tracey Spinks
Ex officio:
Art Tipton
Ronda Thompson
Debby Woodard

Meetings Committee

Charge: Secure top-notch leaders of interest to CRS members as speakers in New York to help increase attendance in 2008.
Chair: Ijeoma Uchegbu
Members:
Raid Alany
Terry Bowersock
Martyn Davies
Nava Dayan
Kam Leong
Sevda Senel
Mark Tracy
Teresa Virgallito
Ex officio: Ronda Thompson

Membership and Development Committee

Charge: Assist with the new membership form and establish a program to transition student members into becoming individual members.
Chair: Mark Tracy
Members:
Diane Burgess
Jian-Xin Li
Siddhesh Patil
Mike Rathbone
Uwe Schote
Teresa Virgallito
Victor Yang
Jonathon Zhao

Ex officio:
Ian Tucker
Ronda Thompson

Nominating Committee
Charge: Find the best possible candidates to run for office for the CRS.
Chair: Randall Mrsny
Members:
Vladimir Torchilin
Ijeoma Uchegbu
Ex officio: Cheryl Sundquist

Pearls of Wisdom
Task: Provide ideas for topics and assist in securing debaters.
Chair: Carla Caramella
Contact:
Ijeoma Uchegbu
Ronda Thompson

Planning and Finance Committee
Charge: Finalize a 2008 budget and begin preparing a three-year budget plan.
Chair: Art Tipton
Members:
Debra Bingham
Irv Jacobs
Tom Redelmeier
Pat Walters
Ex officio: Barbara Mock

Publications Committee
Charge: Continue preparing the best *Newsletter*, propose a plan for establishing a monthly *Newsletter*, and suggest book titles and authors to publish.
Chair: Ijeoma Uchegbu
Book Publishing Committee Chair: Mike Rathbone
Member: Martyn Davies
Journal Committee Chair: Diane Burgess
Newsletter Committee Chair: Yvonne Perrie
Members:
Steven Giannos
Jamileh Lakkis
Arlene McDowell
Bozena Michniak-Kohn
Rod Walker
Ex officio: Jody Grider

Satellite Meeting Review Committee
Charge: Review satellite meeting applications as received and make final recommendations.
Chair: Terry Bowersock
Members:
Marcus Brewster
Karsten Cremer
Doug Dale
Paul Gellert
Dody Reimer
Art Tipton
Ex officio:
Ijeoma Uchegbu
Ronda Thompson

Session Moderator
Task: Assist in securing annual meeting moderators and serve as moderators.
Contact:
Ijeoma Uchegbu
Ronda Thompson

Veterinary Committee
Charge: Increase awareness of CRS outside of the Vet Committee and keep CRS membership informed about the leaders in veterinary-related fields who are leaders in their fields of delivery and use of bioactives.
Chairs:
Arlene McDowell
Sevda Senel
Members:
Marilyn Martinez
Erwin Mombarg
Ramesh Panchagnula
Nicole Schumacher
Contact: Keith Ellis
Ex officio:
Ian Tucker
Ronda Thompson

Workshop Review Committee
Charge: Review workshop meeting applications as received and make final recommendations.
Chair: Terry Bowersock
Members:
Marcus Brewster
Karsten Cremer
Doug Dale
Paul Gellert
Ram Mahato
Dody Reimer
Ron Smith
Art Tipton
Ex officio:
Ijeoma Uchegbu
Ronda Thompson ■

InTheNews

Compiled by Steven Giannos
Industrial Editor

QLT Acquires Leading Edge Ocular Drug Delivery System from ForSight Labs

CNW: October 9, 2007 – VANCOUVER, B.C. – QLT Inc. (NASDAQ: QLTI; TSX: QLT) has announced that it has entered into an agreement under which QLT will acquire privately held ForSight Newco II, Inc. The acquisition includes ForSight Newco II's proprietary ocular punctal plug drug delivery system with the potential for future multi-product opportunities. The first clinical candidate utilizing this leading-edge platform technology will target glaucoma. "We are very excited to work with the experienced drug and device development teams at QLT to advance this technology," said Eugene de Juan Jr., M.D., founder and vice-chair of ForSight Labs. "We think this is a very significant technology that could ultimately lead to a sea of change in the way medications are delivered to the eye."

ForSight Newco II's proprietary punctal plugs are a non-invasive drug delivery system capable of delivering a variety of drugs to the eye over time through controlled release to the tear film. Sustained release punctal plugs could potentially replace eye drops for glaucoma, dry eye, allergies, and postoperative care, which represent a $6 billion market. In addition, plugs may provide a more effective, convenient and reliable treatment alternative that could ultimately improve patient compliance with their medication and outcomes for their disease.

Through this acquisition, QLT, through its wholly-owned subsidiary, will obtain worldwide rights to commercialize ForSight Newco II's proprietary punctal plug technology combined with any active pharmaceutical ingredient and will lead and fund future development efforts in this program. QLT plans to initiate a Phase I/II clinical trial with the first product using ForSight Newco II's proprietary technology for the treatment of glaucoma in the first half of 2008. Glaucoma affects approximately 65 million people worldwide and is the second leading cause of blindness. Approximately 99% of glaucoma patients are treated with topical medications, 4–6% receive surgery, and on average each diagnosed patient has multiple visits to an ophthalmologist each year. Compliance with topical eye drop medications in glaucoma patients is poor, with approximately half of treated patients not refilling their prescription after the first six months of therapy. In spite of this, the glaucoma market continues to grow and in the United States represents a $1.7 billion market.

Researchers Create Modular, Multi-functional Drug Delivery System

Medical Research News: October 8, 2007 – There are two aspects to creating an effective drug: finding a chemical compound that has the desired biological effect and minimal side-effects and then delivering it to the right place in the body for it to do its job. With the support from a $478,000, five-year CAREER award from the National Science Foundation, Eva Harth is tackling the second part of this problem. She is creating a modular, multi-functional drug delivery system that promises simultaneously to enhance the effectiveness and reduce the undesirable side-effects of a number drugs. (NSF's Faculty Early Career Development awards are the agency's most prestigious honor for junior faculty members and are given to individuals judged most likely to become the academic leaders of the 21st century.)

Harth, who is an assistant professor of chemistry at Vanderbilt University, has created a "nanosponge" specially designed to carry large numbers of drug molecules. She has also discovered a "molecular transporter" that, when attached to the nanosponge, carries it and its cargo across biological barriers into specific intracellular compartments, which are very difficult places for most drugs to reach. She has shown that her system can reach another difficult target: the brain. Experiments have shown that it can pass through the brain-blood barrier. In addition, she has successfully attached a special "targeting unit" that delivers drugs to the surface of tumors in the lungs, brain, and spinal cord and developed a "light kit" for her delivery system—fluorescent tags that researchers can use to monitor where it goes.

Harth has taken a different approach from other researchers working on nanotechnology for drug development. Instead of trying to encapsulate drugs in nanoscale containers, she decided to create a nanoparticle that had a large number of surface sites where drug molecules could be attached. To do so, she adopted a method that uses extensive internal cross-linking to scrunch a long, linear molecule into a sphere about 10 nm in diameter, about the size of a protein. Nanoparticles like this are called nanosponges. "We can really load this up with a large number of drug molecules," she stated.

Working with Heidi Hamm, the Earl W. Sutherland Jr. Professor of Pharmacology at Vanderbilt, Harth synthesized a dendritic molecule with the ability to slip through cell membranes and reach the cell nucleus. They figured out how to attach this "transporter" to her nanoparticle and showed that the transporter can pull the nanoparticle after it into cellular compartments. They also demonstrated that the transporter can deliver large molecules—specifically peptides and proteins—into specific sub-cellular locations. "Eva's methods for drug delivery are very novel and versatile and can be adapted to delivery of proteins, peptides, DNA and smaller chemical compounds like most drugs. The breadth of applications makes her technology very powerful," Hamm said.

The chemist is also collaborating with Dennis E. Hallahan, professor of radiation oncology at Vanderbilt, to apply the drug delivery system to fighting cancer. Hallahan's lab has identified a molecule that targets a surface feature on lung carcinomas. Harth took the molecule,

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improved it, attached it to her nanoparticle, and the two of them determined that the combination is capable of delivering drugs to the surface of lung tumors. She is now working with Hallahan to adapt her delivery system to carry cisplatinum, a traditional chemotherapy agent that is used to treat a number of different kinds of cancer but is highly toxic and has a number of unpleasant side effects. By delivering the anti-cancer agent directly to the cancerous tissues, Eva's system decreases the adverse effects on other tissues and increases its potency by delivering a higher concentration of the drug directly on the cancer, Hallahan explained. "The people in my lab have tried…a number of different drug delivery systems and Eva's works the best of those we've looked at," Hallahan said. Vanderbilt is applying for two patents on the system.

Sontra Medical Corporation Changes Name to Echo Therapeutics, Inc.

PRNewswire-FirstCall: October 5, 2007, FRANKLIN, Mass. – Following its recent merger with Echo Therapeutics, Inc., Sontra Medical Corporation (OTC Bulletin Board: SONT – News), a dual platform-enabled transdermal specialty therapeutics and diagnostics company, has announced that it has changed its corporate name to Echo Therapeutics, Inc., effective Monday, October 8, 2007. In addition, on October 8, 2007, the Company's OTC Bulletin Board ticker symbol will change to "ECTE," and its corporate website address will become www.echotx.com. "Our new name better reflects our expanded strategic focus on building a broad pipeline of advanced topical formulations of FDA-approved specialty pharmaceutical products and next generation needle-free transdermal diagnostics," said Patrick T. Mooney, M. D., CEO of Echo Therapeutics.

New Drugs Study Findings Published by M. Schär-Korting and Colleagues

Drug Week via NewsEdge Corporation (NewsRx.com): October 4, 2007 – Investigators have published new data in the report "Lipid Nanoparticles for Improved Topical Application of Drugs for Skin Diseases." "Due to the lower risk of systemic side effects, topical treatment of skin disease appears favourable, yet the stratum corneum counteracts the penetration of xenobiotics into viable skin. Particulate carrier systems may mean an option to improve dermal penetration," scientists wrote in the *Advanced Drug Delivery Reviews* report.

"Since epidermal lipids are found in high amounts within the penetration barrier, lipid carriers attaching themselves to the skin surface and allowing lipid exchange between the outermost layers of the stratum corneum and the carrier appear promising. Besides liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been studied intensively. Here we describe the potential of these carrier systems and compare the dermal uptake from SLN and NLC to the one of alternative vehicle systems," wrote M. Schär-Korting and colleagues. The researchers concluded, "A special focus is upon the interactions of active ingredients and the lipid matrix as well as the quantification of dermal penetration."

Schär-Korting and colleagues published their study in *Advanced Drug Delivery Reviews* (Lipid nanoparticles for improved topical application of drugs for skin diseases. Advanced Drug Delivery Reviews, 2007;59(6):427-443). Additional information can be obtained by contacting M. Schär-Korting, Institut fur Pharmazie, Pharmakologie und Toxikologie, der Freien Universitat Berlin, D-14195 Berlin, Germany.

Research from Heinrich-Heine University, Institute of Pharmaceutics and Biopharmaceutics, Provides New Data on Biopharmaceuticals

Health & Medicine Week via NewsEdge Corporation (NewsRx.com): October 4, 2007 – Scientists discuss in "Solid Lipid Extrusion of Sustained Release Dosage Forms" new findings in biopharmaceuticals. "The applicability of the solid lipid extrusion process as preparations method for sustained release dosage forms was investigated in this study. Two lipids with similar melting ranges but of different composition, glyceryl palmitostearate (Precirol ATO 5) and glyceryl trimyristate (Dynasan 114), and mixtures of each lipid with 50% or 75% theophylline were extruded at temperatures below their melting ranges," scientists in Germany reported.

"Extrudates were analyzed using differential scanning calorimetry, scanning electron microscopy, porosity measurements and in vitro drug dissolution studies. The possibility of processing lipids by softening instead of complete melting and without subsequent formation of low-melting, metastable polymorphs could be demonstrated. Extrudates based on formulations of glyceryl palmitostearate/theophylline (50:50) and glyceryl trimyristate/ theophylline (50:50) showed sustained release properties. An influence of extrusion conditions on the matrix structure was shown for extrudates based on a mixture of glyceryl trimyristate and theophylline (50:50). Glyceryl trimyristate tended to solidify in porous structures after melting. Exceeding a material temperature of 50.5 degrees C led to porous extrudate matrices with a faster drug release. The production of novel, non porous sustained release matrices was possible at a material temperature of 49.5 degrees C," wrote C. Reitz and colleagues at Heinrich-Heine University, Institute of Pharmaceutics and Biopharmaceutics. The researchers concluded, "Extrudates based on glyceryl trimyristate/theophylline (50:50) [showed] only slight changes in melting enthalpy and stable drug release profiles."

Reitz and colleagues published their study in the *European Journal of Pharmaceutics and Biopharmaceutics* (Solid lipid extrusion of sustained release dosage forms. European Journal of Pharmaceutics and Biopharmaceutics, 2007;67(2):440-448). For additional information, contact C. Reitz, Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany.

Research Results from Kyushu Institute of Technology

Drug Week via NewsEdge Corporation (NewsRx.com): October 4, 2007 – According to recent research published in the *European Journal of Pharmaceutics and Biopharmaceutics*, "A stick-type long lasting device for both transdermal and topical drug delivery has been developed. Ketotifen fumarate (KT) was used as a model drug." "The effect of a variety of

permeation enhancers was investigated using hairless mouse skin in vitro. Polyoxyethylene oleyl ether (POE), among the enhancers used, most enhanced the skin permeation of KT. The permeation enhancement was mainly due to the increase in the drug solubility in the stratum corneum and the resulting increase in the partition coefficient," wrote C. Kimura and colleagues at Kyushu Institute of Technology. The researchers concluded, "The rate of skin permeation of KT was approximately proportional to the loading dose of the drug."

Kimura and colleagues published their study in the *European Journal of Pharmaceutics and Biopharmaceutics* (Skin permeation of ketotifen applied from stick-type formulation. European Journal of Pharmaceutics and Biopharmaceutics, 2007;67(2):420-424). For additional information, contact C. Kimura, College of Computer Science and Systems Engineering, Kyushu Institute of Technology, Fukuoka, Japan.

New Drug Delivery Study Findings Published by Researchers at Tehran University of Medical Sciences

Drug Week via NewsEdge Corporation (NewsRx.com): October 4, 2007 – A new study on "Solid carriers for improved solubility of glipizide in osmotically controlled oral drug delivery system," is now available. "The purpose of this study was to increase the solubility of glipizide (gli) by solid dispersions SDs technique with polyvinylpyrrolidone (PVP) in aqueous media. The gli-PVP solid dispersion systems was prepared by physical mixing or spray drying method, and characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRD) analysis, Fourier transformation-infrared spectroscopy (FT-IR) and scanning electron microscopy (SEM)," scientists wrote in the *Drug Development and Industrial Pharmacy* report.

"The elementary osmotic pumps (EOPs) were prepared with gli-PVP complex and the effect of the PVP percentages on the enhancing of gli dissolution rate was studied. The influences of various parameters e.g., drug-PVP ratio, level of solubility modifier, coating weight gain and diameter of drug releasing orifice on drug release profiles were also investigated. The solubility and dissolution rates of gli were significantly increased by solid dispersion using [a] spray dried method as well as their physical mixture," wrote A. Mehramizi and colleagues at Tehran University of Medical Sciences. The researchers concluded, "The obtained results indicated that gli-PVP solid dispersion system has suitable solubility behavior in EOP tablets."

Mehramizi and colleagues published their study in *Drug Development and Industrial Pharmacy* (Solid carriers for improved solubility of glipizide in osmotically controlled oral drug delivery system. Drug Development and Industrial Pharmacy, 2007;33(8):812-823). Additional information can be obtained by contacting A. Mehramizi, Tehran University of Medical Sciences, School of pharmacy, Tehran, Iran.

MacroChem Acquires Rights to Pexiganan, a Novel Topical Anti-infective for Treatment of Diabetic Foot Infections, from Genaera

PR Newswire via NewsEdge Corporation (PRNewswire-FirstCall): October 3, 2007, WELLESLEY HILLS, Mass. – MacroChem Corporation (OTC Bulletin Board: MACM) today announced that it has exercised the option it acquired in July 2007 to acquire exclusive worldwide license rights for drug uses of pexiganan, a novel, small peptide anti-infective for treatment of patients with mild diabetic foot infection (DFI), from Genaera Corporation.

"We believe this is a unique opportunity for MacroChem to broaden its product portfolio with a product that has already completed two Phase 3 clinical trials and that fits our strategic focus and complements our lead product candidate, EcoNail® for treatment of nail fungus," stated Robert J. DeLuccia, president and CEO of MacroChem. "Both drugs would treat diseases of the foot predominantly treated by the same prescribing specialists, namely podiatrists. Both EcoNail and pexiganan are potentially of interest to a larger number of physician specialists and primary care physicians. MacroChem would ultimately be seeking a partner to market to those groups while retaining rights to market to selected physician specialists." "We are pleased to enter into an agreement with MacroChem Corporation for the therapeutic rights to pexiganan. This agreement reflects a first step in the execution of Genaera's strategy to divest its non-core-assets, including Squalamine and LOMUCIN™. We believe pexiganan has significant potential to treat infected diabetic foot ulcers and that MacroChem is dedicated to the commercialization of this asset," stated Dr. Henry Wolfe, executive vice president and chief scientific officer of Genaera.

Cerimon Pharmaceuticals Initiates Phase I Clinical Study of Topical Diclofenac Sodium Patch

PR Newswire via NewsEdge Corporation (PRNewswire): October 2, 2007, SOUTH SAN FRANCISCO, Calif. – Cerimon Pharmaceuticals, Inc., announced that it has initiated a Phase I clinical study of a novel diclofenac sodium patch, the company's lead pain asset. The study will evaluate safety, tolerability, and systemic pharmacokinetics of a topical patch formulation of diclofenac sodium, a non-steroidal anti-inflammatory drug (NSAID), in 16 healthy volunteers. The Phase I study is expected to be completed in the fourth quarter of 2007. Following the completion of this study, Cerimon plans to rapidly initiate late-stage efficacy and safety studies of its diclofenac sodium patch in patients with acute musculoskeletal pain.

"Topical diclofenac is the second therapeutic product Cerimon has advanced into clinical studies this year, following the initiation of Phase IIb testing for Simulect® (basiliximab) in the first quarter," stated Paul Sekhri, president and CEO of Cerimon Pharmaceuticals. "We are proud of this progress and believe the diclofenac patch will address the market need for safe and effective topical pain therapies. Currently, topical NSAIDs are marketed in Europe, Japan, and other parts of the world, but not in the U.S. Their advantage in treating musculoskeletal pain is the ability to deliver drug directly to the affected area with minimal systemic exposure. Given the systemic side effects of traditional non-topical NSAIDs, as well as the withdrawal of some COX-2 inhibitors, we believe developing a new treatment option

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is an important goal for the medical community."

Triggered Release of Liposomal Drugs Following Mixing of Cationic and Anionic Liposomes

U.S. Patents via NewsEdge Corporation: October 2, 2007; Pub. Number: US7273620; Appl. Data: 10 20030519; Applicant: University of British Columbia; Inventor(s): Zhigaltsev, Igor V. Wong, Kim F., Maurer, Norbert Cullis, Pieter R.; Title: Triggered Release of Liposomal Drugs Following Mixing of Cationic and Anionic Liposomes; Abstract: Methods and compositions for triggering the delivery of an encapsulated therapeutic agent from a liposome are provided. Liposomes of opposite charge and incorporating lipids which favor non-lamellar structures are contacted in vivo. At least one of the liposome encapsulates at least one therapeutic drug or agent. Preferably, the liposomes have a fusogenic hydrophillic coating, such as PEG, to control the rate of interaction of the liposomes and release of the therapeutic agent.

Transdel Pharmaceuticals, Inc. Completes Merger Transaction, Equity Financing, and Begins Trading Under Symbol "TDLP"

Market Wire via NewsEdge Corporation: October 1, 2007, LA JOLLA, Calif. – Transdel Pharmaceuticals, Inc. (OTCBB: TDLP), a specialty pharmaceutical company focused on the development and commercialization of non-invasive topically targeted medications, has announced the completion of a merger transaction and the commencement of trading under the symbol "TDLP" on the Over the Counter Bulletin Board. In connection with the merger on September 17, 2007, the company raised $4.0 million through the sale of common stock and warrants. The proceeds will be used for the further development of the company's lead drug, Ketotransdel™, a novel topical cream-based non-steroidal anti-inflammatory drug (NSAID) for pain.

Ketotransdel™ is composed of a transdermal formulation of ketoprofen, an NSAID, and the Company's innovative proprietary Transdel™ drug delivery system. Ketotransdel™ penetrates the skin barrier to reach the targeted underlying tissue, where it exerts its prolonged localized anti-inflammatory effect. This drug may minimize systemic exposure, resulting in fewer concerns pertaining to gastrointestinal, renal, cardiovascular, and other adverse systemic effects, which are associated with orally administered NSAIDs. This drug may help address certain safety concerns in the market and potentially provide physicians and patients with a much needed alternative for pain.

Dr. Juliet Singh, president and chief executive officer of Transdel Pharmaceuticals, stated, "I am pleased to have completed this transaction as it enables us to broaden our investor base and create a liquid market for our stock. It also gives us the opportunity to access the market to financially support the completion of the required Ketotransdel™ clinical trials for FDA approval and to continue the development of our pipeline." Dr. Singh continued, "We are completely focused on leveraging the Company's versatile proprietary Transdel™ drug delivery platform and capital efficient business model to increase shareholder value. With a proven and experienced management team, strong intellectual property and the utilization of the most experienced contract organizations known in the field, we believe that the Company is well positioned to advance the development of its lead drug Ketotransdel™."

Macroflux Announces Name Change to Zosano Pharma, Inc.

Business Wire: September 27, 2007, FREMONT, Calif. – The Macroflux Corporation announced that it has changed the name of the company to Zosano Pharma, Inc. "Our name change reflects the positive evolutionary steps the company is taking to advance our innovative transdermal microprojection delivery system technology," said M. Cory Zwerling, CEO and president of Zosano Pharma.

The Zosano name is a combination of "sano," which means to heal or to cure, and "zo," for zone. The healing zone is where Zosano will focus efforts to create improved pharmaceutical products utilizing our innovative drug delivery technology. Zosano's Macroflux® transdermal microprojection delivery system provides unique benefits, including convenient needle-free administration with room-temperature stability for various therapeutic peptides, proteins, small molecules, and vaccines.

"Our transdermal system has been clinically tested in over 300 patients with four different peptides and a vaccine," said Peter Daddona, Ph.D., and chief scientific officer for Zosano. "In addition to product convenience and stability benefits, the system provides rapid and efficient drug delivery beyond existing injectable products."

Zosano Pharma's lead program, Zosano™ PTH, is in Phase II development for osteoporosis. The trial is scheduled for completion in mid 2008. Zosano is pursuing a regulatory process that leverages existing PTH safety and efficacy data. The Zosano PTH will be an important contributor to anabolic treatment or bone-building options in the large global osteoporosis market, giving physicians a convenient and stable product for older women and men who currently must use daily injections.

Zosano Pharma was founded in October 2006. The company secured a significant financial commitment of $90 million from four venture companies to advance this drug delivery technology and has established a formidable intellectual property (IP) position in this arena. "With this strong financial backing, substantive IP positions, exciting technology and an experienced Board, we have been able to focus on further developing and implementing our product development strategy," said Zwerling.

Javelin Pharmaceuticals, Inc. Granted Commercially Important U.S. Patent for Intranasal Ketamine

Business Wire via NewsEdge Corporation: September 27, 2007, CAMBRIDGE, Mass. – Javelin Pharmaceuticals, Inc. (Amex: JAV - News) was granted a commercially important U.S. patent, enabling greater protection of Javelin's PMI-150 (intranasal ketamine). U.S. Patent Number 7,273,889, entitled "NMDA Receptor Antagonist Formulation with Reduced Neurotoxicity," extends protection covering Javelin's intranasal ketamine drug candidates into 2023.

"This new patent, directed to Javelin's anticipated commercial formulations, recognizes Javelin's continuing ability to develop first in class, novel pharmaceutical product formulations to address unmet medical needs in the acute pain care market," said Dr. Mermelstein. "Upon approval, PMI-150 will be the only intranasal ketamine product offering physicians and patients a non-opioid alternative for treatment of moderate to severe pain. It will be well-suited for both civilian and military use in medically supervised settings." Dr. Mermelstein added, "Supplemental New Drug Applications are planned for PMI-150 to include use as an adjuvant to opioids and for breakthrough cancer pain. We look forward to our pre-NDA meeting with the FDA, currently scheduled for November and anticipate filing our NDA for PMI-150 in mid-2008, so today's news is very exciting for the program and shareholders alike."

Exelon Patch Receives EU Approval, the First Skin Patch Therapy to Treat Alzheimer's Disease

Hugin via NewsEdge Corporation: September 24, 2007, BASEL, Switzerland – The European Commission has approved the Exelon patch (rivastigmine transdermal patch), an innovative way to deliver this effective medicine to patients suffering from mild to moderately severe Alzheimer's disease. Exelon patch is the first and only transdermal treatment for Alzheimer's disease, a degenerative brain disorder affecting 18 million people worldwide and the third leading cause of death behind cardiovascular disease and cancer. The skin patch is applied once daily to the back, chest, or upper arm of the patient.

"Exelon patch represents a therapeutic innovation that is designed specifically to meet the needs of patients, caregivers and physicians involved with this devastating disease," said James Shannon, MD, global head of development at Novartis Pharma AG. "The patch has been shown to increase compliance, reduce side effects, and allow medication to be delivered through the skin into the bloodstream smoothly and continuously over 24 hours, helping to achieve optimal dosing. All these benefits offer the potential for improved outcomes in patients," Shannon said.

The EU approval, coming soon after the U. S. approval in July 2007, was based on results from the international IDEAL (Investigation of Transdermal Exelon in Alzheimer's Disease) study, which involved nearly 1,200 patients with mild to moderate Alzheimer's disease. The patch showed similar efficacy to the highest doses of Exelon capsules, as well as significant improvement in memory and the ability to perform everyday activities compared with placebo. In addition, the IDEAL study demonstrated three times fewer reports of gastrointestinal side-effects (nausea and vomiting) with the patch than the oral form of the medication.

Exelon (rivastigmine) in capsule form has been approved since 1997 to treat patients with mild to moderate Alzheimer's disease in more than 70 countries. Since 2006, Exelon in capsule form or oral solution has been the only member of the cholinesterase inhibitor class of medicines that is approved in both Europe and the United States for treating mild to moderate Alzheimer's disease as well as Parkinson's disease dementia. On July 6, 2007, the U.S. Food and Drug Administration (FDA) approved Exelon patch (rivastigmine transdermal system) for the treatment of mild to moderate Alzheimer's disease and Parkinson's disease dementia. Alzheimer's disease affects one in 10 people over age 65, making it the most common form of dementia. The global direct costs of dementia in 2003, for example, were estimated at US$156 billion.

Researchers from The Pennsylvania State University Discuss Findings in Drug Delivery

Drug Week via NewsEdge Corporation (NewsRx.com): September 20, 2007 – According to recent research published in *Pharmaceutical Research*, in previous studies, ultrasound mediated transdermal drug delivery has shown a promising potential as a method for noninvasive drug administration. For prospective future human application, a study was designed to determine the feasibility of a lightweight cymbal transducer array as a practical device for noninvasive transdermal insulin delivery in large pigs.

"The results indicate the feasibility of ultrasound mediated transdermal insulin delivery using the cymbal transducer array in animal with a similar size and weight to a human," wrote E. J. Park and colleagues, The Pennsylvania State University. The researchers concluded, "Based on these result[s], the cymbal array has potential as a practical ultrasound system for noninvasive transdermal insulin delivery for diabetes management."

Park and colleagues published their study in *Pharmaceutical Research* (Ultrasound mediated transdermal insulin delivery in pigs using a lightweight transducer. Pharmaceutical Research, 2007;24(7):1396-1401).

Crospon Licenses HP Technology to Create Industry-First Skin Patch for "Smart" Drug Delivery

Drug Week via NewsEdge Corporation (NewsRx.com): September 20, 2007 – HP (NYSE:HPQ) and Crospon, a medical device developer based in Galway, Ireland, announced they have entered a licensing agreement for a drug delivery platform that enables painless, controlled release of one or more drugs in a single patch applied to the skin. Under the agreement, HP will license its intellectual property to Crospon in return for royalty payments. Crospon will commercialize the patch, which was invented by HP Labs, the company's central research facility, and make it available to pharmaceutical companies to use in various therapeutic areas. Crospon, which recently announced the finalization of €2.3 million in seed financing, will manufacture the skin patch and manage all marketing, sales, and support of the technology.

The patch delivers medication intradermally—just below the surface of the skin—and enables precise control of dosage timing, access to dosage history, patient activation mechanisms, and inherent safety protocols for preventing adverse drug interactions. Transdermal patches (which rely on absorption through the skin) for nicotine delivery have become a mainstay for smoking cessation programs; however, they have not been a widely effective delivery mechanism for many drugs because the skin acts as a natural barrier.

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The HP-developed skin patch uses microneedles that barely penetrate the skin; this radically reduces discomfort compared with traditional hypodermic needles and enables the technique to be used with a much wider variety of drugs and biopharmaceuticals. The microneedles allow medication to quickly enter the bloodstream, resulting in the potential delivery of lower and more precise dosages. HP initially developed the drug delivery technology as a way to repurpose its inkjet technology for use in new markets. The technology in the skin patch is similar to that employed in HP's patented process for its inkjet cartridges. "This industry-first skin patch invented by HP allows Crospon to offer a superior drug delivery platform for doctors and patients," said John O'Dea, chief executive officer, Crospon. "We look forward to working with our pharmaceutical customers to bring this breakthrough solution to the market."

The agreement between HP and Crospon resulted in part from HP's relationship with Enterprise Ireland, an Irish government agency tasked with supporting and growing indigenous business in Ireland. Through Enterprise Ireland, companies can license the intellectual property of HP and access the company's business and technology mentoring. "We encourage companies like Crospon to apply HP's intellectual property in innovative ways to help more people benefit from these important technologies," said Joe Beyers, vice president, Intellectual Property Licensing, HP. "By licensing core intellectual property in thermal inkjet technology for use in a drug delivery product, HP breathes new life into its mature technology while capitalizing on the booming healthcare and life sciences market."

HP encourages other organizations worldwide to leverage its vast research and development network and portfolio of nearly 30,000 patents to bring new technologies to market through intellectual property licensing agreements. These agreements also enable HP to generate a return on its R&D investment through licensing fees and royalties. More information on HP's intellectual property licensing program is available at www.hp.com/hpinfo/abouthp/iplicensing/. Images of the prototype drug delivery platform are available at www.hpl.hp.com/about/media/drug_delivery/.

New Topical Therapy Safely Treats Serious Skin Infections Without Systemic Side Effects

Bioterrorism Week via NewsEdge Corporation (NewsRx.com): September 20, 2007 – A new topical lotion that penetrates the skin deeply enough to target and eliminate serious skin infections, but without being systemically absorbed, has shown a high degree of safety and tolerability in patients with onychomycosis, or toenail fungus, a new study has shown.

"Results of the phase 1 clinical trial are important to the fields of dermatology and infectious diseases because currently approved systemic medications for onychomycosis carry serious risks of cardiac and liver toxicity," said James Baker, MD, chief science officer and founder of NanoBio Corporation in Ann Arbor, Michigan. NanoBio scientists developed the lotion. The phase 1 data for the new lotion, NB-002, was presented at the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting, held September 17–20, 2007, in Chicago.

NanoBio Corporation is a spin-off from the University of Michigan. The company develops novel anti-infective products and mucosal vaccines to treat or prevent a wide range of infections, from cold sores and toenail fungus to influenza and hepatitis B. Its lead products are NB-001 to treat herpes labialis and NB-002 to treat onychomycosis. NB-002 is a topical oil-in-water nanoemulsion combined with an antimicrobial agent commonly used in oral products to treat gingivitis and other conditions of the mouth and throat. The nanoemulsion undergoes a high-energy process to shrink or "nano-size" the particles so they are small enough to enter the skin through pores and hair follicles but too large to penetrate the tight junctions of the epithelium. As a result, NB-002 is not systemically absorbed, as the phase 1 study has demonstrated.

Results of a phase 2 clinical trial for onychomycosis are expected in early 2008. In addition to its topical agents, NanoBio is developing a rich pipeline of needle-free vaccines based on using the same oil-in-water emulsion technology as an adjuvant. Mucosal vaccines against influenza and hepatitis are scheduled for human testing beginning next year, while an anthrax vaccine has demonstrated safety and strong efficacy in animal studies.

Reports from University of Parma Highlight Recent Research

Drug Week via NewsEdge Corporation (NewsRx.com): September 20, 2007 – According to recent research from Parma, Italy, "We have recently described an innovative drug delivery system, a water-based and vapor permeable film intended for dermal and/or transdermal delivery. The aim of this work was to modulate the delivery of the model drug lidocaine hydrochloride from the transdermal film across rabbit ear skin."

"The effect of drug loading, of film-forming polymer type and content, of adhesive and plasticizer on lidocaine transport across the skin was evaluated. An additional objective was to evaluate the effect of occlusion on the kinetics of lidocaine transport, by applying an occlusive backing on the surface of the transdermal film. From the data obtained it can be concluded that the transdermal film acts as a matrix controlling drug delivery. The film-forming polymer molecular weight had a negligible effect on drug penetration, while its content was more effective. The choice of the adhesive seems to be the most important variable governing drug transport. In particular, the presence of lauric acid combined with a basic drug, such as lidocaine, can produce a relevant improvement in permeation, because of the formation of an ion pair," wrote C. Padula and colleagues, University of Parma. The researchers concluded, "Concerning the kinetics, drug depletion is responsible for the declining permeation rates observed in the late times of permeation."

Padula and colleagues published their study in the *European Journal of Pharmaceutics and Biopharmaceutics* (Single-layer transdermal film containing lidocaine: Modulation of drug release. European Journal of Pharmaceutics and Biopharmaceutics, 2007;66(3):422-428). For additional information, contact P. Santi, University of Parma, Department of

Pharmacy, Viale GP Usberti 27-A, I-43100 Parma, Italy.

Adams Respiratory Therapeutics and Lipocine Enter into License and Collaboration Agreement

PR Newswire via NewsEdge Corporation: September 19, 2007, CHESTER, N.J., and SALT LAKE CITY, Utah – Adams Respiratory Therapeutics, Inc. (Nasdaq: ARxT) and Lipocine Inc., a privately-held, leading drug delivery company that uses clinically validated proprietary technologies to address key unmet drug delivery and therapeutics needs, announced that they have entered into a license and collaboration agreement to develop new prescription adult cough products.

Commenting on the agreement, COO Robert D. Casale said, "This collaboration with Lipocine provides Adams with access to an additional proprietary platform technology and fits with our strategy of taking established compounds and adding increased functionality to create patent-protected, value-added products. The products developed through this collaboration could offer doctors a non-narcotic prescribing option to treat cough with an enhanced dosing regimen. In addition, these products will help Adams compete in the $1.1 billion prescription cough and cold market in the United States." "Given the large and growing size of the respiratory market, and how patients can benefit from enhanced dosage forms and regimens, we are very pleased to partner with Adams, a company highly respected for its commercialization accomplishments," said Dr. Mahesh Patel, president and CEO of Lipocine Inc.

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

Skin Patch Stops Travelers' Diarrhea: Study

Agence France-Presse English Wire via NewsEdge Corporation (AFP): September 19, 2007, CHICAGO, Ill. – Scientists have announced a skin-patch vaccine that can save the wearer from the rumblings of diarrhea when traveling to places where stomach bugs are endemic. A clinical trial by Maryland-based vaccine maker Iomai Corporation showed that of 59 people who used the patch—which is slapped on the skin to deliver the vaccine without a needle—only 3 found their guts growling with diarrhea. Comparing this to results for travelers who were given a placebo, the test showed that the patch cut outbreaks of diarrhea by three-quarters.

"These are clinically significant results that suggest that the patch vaccine will address the most significant unmet need for travel medicine: prophylaxis for travelers' diarrhea," said Gregory Glenn, the company's chief scientific officer. "Those who received the Iomai vaccination were much less likely to get sick, and those who were sickened had far milder illness than those who received a placebo."

The findings were presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in Chicago. "The results presented at ICAAC are the most robust ever shown in the prevention of travelers' diarrhea," said Herbert DuPont, a doctor from the Center for Infectious Diseases at the University of Texas, who led the trial. "They suggest we may be near a turning point in the prevention of this common, often serious disease." The condition, sometimes known as "Delhi belly" for its association with sickly tourists in India, strikes some 20 million travelers a year. The bugs are common in Africa, Asia, and Latin America. Iomai, citing the World Health Organization, said the bacteria kills 380,000 people each year in poor countries. Its most common cause is the "enterotoxigenic *E. coli* bacteria," the company said. The patch delivers a toxin caused by the bacteria safely through the skin to trigger an immune response.

The phase II trial headed by DuPont was carried out on 170 volunteers who wore the patches before traveling to Mexico and Guatemala. One further phase of clinical trials is required before the patch can be marketed. Iomai plans to start these phase III trials in 2008. Its chief executive Stanley Erck, quoted in the statement, valued the potential market for an effective diarrhea treatment at 750 million dollars a year.

New Drug Delivery Study Findings Have Been Reported by Researchers at Trinity College

Drug Week via NewsEdge Corporation (NewsRx.com): September 13, 2007 – Investigators have published new data in the report "Combined Effects of Iontophoretic and Chemical Enhancement on Drug Delivery. II. Transport Across Human and Murine Skin." This paper reports measurements of the release characteristics of the model drug salbutamol from a liquid crystalline vehicle across both human and hairless murine skin *in vitro*. "The use of oleic acid and iontophoresis as penetration enhancement techniques, used separately and simultaneously, was also investigated," scientists reported in the *International Journal of Pharmaceutics*.

"Over a period of 12h, salbutamol base did not diffuse from the vehicle across excised human skin while, in contrast, over a period of 2h, the drug passively transported across hairless murine skin. A current of density of 0.39mAcm(-2) facilitated a significant transport of salbutamol from the liquid crystalline vehicle across excised human skin but with a small (<0.1) transport number. The quantity of salbutamol transported across excised hairless murine skin under the same conditions was significantly greater with a transport number of 0.68. The alteration of the permeability of the tissue was less than that of the human skin and a full recovery of the pre-iontophoretic permeability of murine skin was consistently observed. The incorporation of either oleic or lauric acid into the monoglyceride component of the vehicle at a concentration of 0.1M had a marked effect on the transport of salbutamol across both human and murine skin. The initial passive permeation of the drug across the skin was not affected but the rate of drug delivery during iontophoresis was typically observed to increase by a factor greater than two. The post-iontophoretic transport of salbutamol across either tissue was also substantially enhanced in the presence of the fatty acid. The analogous use of stearic acid did not significantly influence the iontophoretic or the post-iontophoretic transport of salbutamol across excised human skin. The investigation also

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revealed a synergistic combination of the fatty acid and anodal iontophoresis to enhance the in vitro transport of other drug substances, including nicotine and diltiazem hydrochloride across murine skin. Oleic acid increased both the iontophoretic and post-iontophoretic transport of nicotine, so that the enhancement of drug delivery was greater than that caused by the current alone," wrote L. M. Nolan and colleagues at Trinity College. The researchers concluded, "The investigation also indicated that the barrier properties of the skin recover following the constant current iontophoresis in the presence of oleic or lauric acids."

Nolan and colleagues published their study in the *International Journal of Pharmaceutics* (Combined effects of iontophoretic and chemical enhancement on drug delivery. II. Transport across human and murine skin. International Journal of Pharmaceutics, 2007;341(1-2):114-124). Additional information can be obtained by contacting L. M. Nolan, School of Chemistry, Trinity College, Dublin 2, Ireland.

Innocoll Enters into Collaboration with TGR Biosciences for Development of a Novel Wound Healing Product

PR Newswire via NewsEdge Corporation: September 12, 2007, ASHBURN, Va. – Innocoll, Inc. announced that its wholly-owned subsidiary, Innocoll Technologies Ltd., has entered into a strategic collaboration with TGR BioSciences Pty Ltd to evaluate the combination of Innocoll's collagen-based drug delivery technology, CollaRx®, with TGR Biosciences' proprietary wound healing compound, TGR-265.

Innocoll's CollaRx® technology platform is a biocompatible and fully bioresorbable collagen matrix for localized drug delivery. It is composed of purified type I fibrillar collagen and can be prepared in the form of a lyophilized sponge or film-cast membrane using a proprietary manufacturing process. Both CollaRx® formats can be surgically implanted or applied topically to wounds, enabling drugs to be delivered locally to the intended site of action and thereby minimize any systemic-related side effects.

CollaRx® matrices are biodegraded by natural enzymatic activity and fully resorbed within a few days or up to several weeks according to the local physiological environment. The *in vivo* release of drug from the CollaRx® matrix takes place via a combination of diffusion and natural breakdown of the collagen to provide both rapid and prolonged release, which can be controlled through formulation techniques and processing variables. The CollaRx® matrix also provides an initial scaffold for cell migration and proliferation, thereby stimulating production of certain cytokines and growth factors and so itself plays an integral role in the repair and replacement of both hard and soft tissue by accelerating tissue granulation and epithelialization.

TGR-265 is a naturally derived bioactive protein that has been shown through extensive *in vitro* and *in vivo* pre-clinical testing to stimulate the fibrogenic response, production of host type 1 collagen and deposition of extracellular matrix. Under the terms of the collaboration, Innocoll will incorporate TGR-265 into the CollaRx® sponge and membrane formats for further evaluation. TGR BioSciences will fund development of the formulated products.

Aradigm and CyDex Sign Development Collaboration Agreement

September 6, 2007, HAYWARD, Calif., and LENEXA, Kans. – Aradigm Corporation (OTC BB: ARDM) and CyDex, Inc. announced they have entered into a two-year collaboration agreement for the development and commercialization of combination products containing inhaled corticosteroids, anticholinergics, and beta-2 agonists for the treatment of asthma and chronic obstructive pulmonary diseases (COPD).

Under the terms of the agreement, the costs of the collaboration projects will be borne 60% by Aradigm and 40% by CyDex, with third-party licensing and sales revenues to be shared in the same ratio. "There is a lot of interest in inhalation products containing a combination of drugs as these have proven to be very popular with millions of asthma and COPD patients," said Igor Gonda, Ph.D., Aradigm's president and CEO. "We are pleased to be working with CyDex – a company with an excellent track record of developing and partnering innovative pharmaceutical products."

John Siebert, CEO of CyDex and a member of Aradigm's Board of Directors, said "Putting together CyDex's aqueous formulation capabilities with Aradigm's palm-size AERx Essence® inhalation delivery system has the potential to generate a family of attractive novel therapies for asthma and COPD patients. We believe that the products containing CyDex's formulations delivered by the AERx Essence technology could become a new treatment of choice for many of these patients." ■

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

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

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

July 12–13, 2008
Oral Drug Delivery: Challenging Patient Groups
Chairs: Daniel Bar-Shalom of Egalet A/S, Denmark
Brigitte Skalsky, Evonik Röhm GmbH, Germany
Clive Wilson, University of Strathclyde, Scotland

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

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calendar of events

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

CRS Australian Chapter 1st AUS-CRS Symposium

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

9th US-Japan Symposium on Drug Delivery

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

59th Indian Pharmaceutical Congress

December 20-23, 2007
Banaras Hindu University
Varanasi, India
www.59thipcvaranasi.com

2008 Arden Conference: Particle and Powder Technologies for Solid Dosage Forms

February 3-8, 2008
The Thayer Hotel
West Point, New York, USA
www.aapspharmaceutica.com/ardenhouse/

Joint Annual Conference of the Association for General and Applied Microbiology and the German Society for Biochemistry and Molecular Biology

March 9-11, 2008
Johann-Wolfgang-Goethe University
Frankfurt/Main, Germany
http://conventus.de/vaam-gbm2008/

35th Annual Meeting of the Controlled Release Society

July 12-16, 2008
Hilton New York
New York City, New York, USA
www.controlledreleasesociety.org

CPT2008

July 27-August 1, 2008
Québec City Convention Centre
Québec City, Québec, Canada
www.cpt2008.org/

World Congress of Pharmacy and Pharmaceutical Sciences 2008

August 29-September 4, 2008
Basel, Switzerland
www.fip.org