CRS Delivering Bioactives

Newsletter

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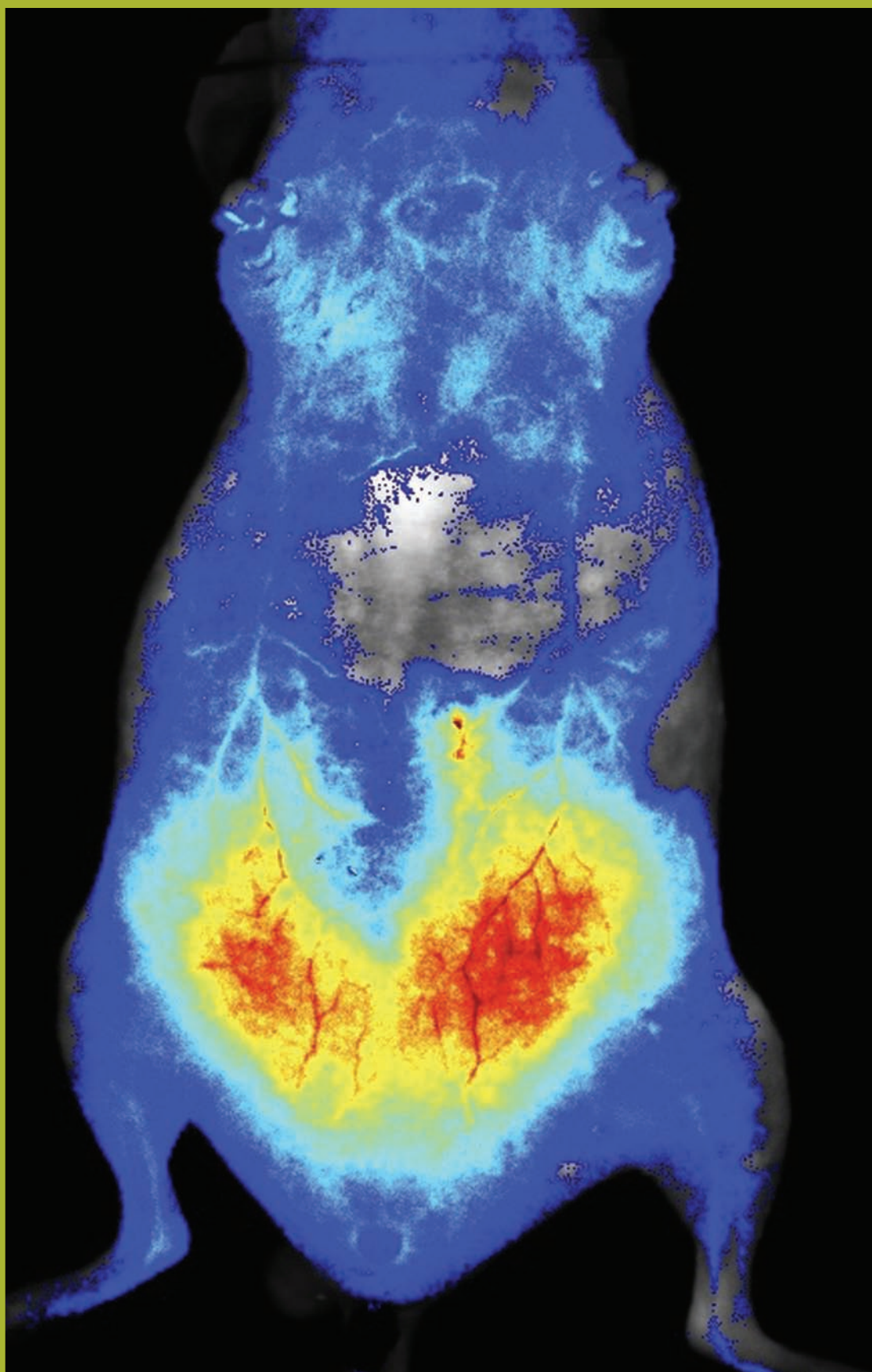
What's Inside



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Delivering Bioactives

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

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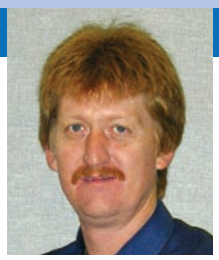
From the Editor



Roderick B. Walker
Rhodes University
Republic of South Africa

Copy to come. ■

Diane J. Burgess, Ph.D.
Board of Trustees Distinguished Professor
School of Pharmacy, University of Connecticut, Storrs, CT, U.S.A.

It takes a village…

As I write this, I am preparing for a meeting that will take place at CRS headquarters in St. Paul, MN. As CRS meetings go, this is a groundbreaking event. By sharing the overall agenda and purpose of the meeting, you will see why my thoughts are so focused on this event.

The CRS board and leadership from all of the CRS committees will be in attendance. The purpose of the meeting is to share an overview of CRS's long-range plans, financial priorities, and goals for 2010–2011. We will also discuss CRS's current initiatives and how the committees fit into the strategic plan. In addition, we (the CRS board) will use this opportunity to solicit committee input and ideas for improving communication, discuss committee priorities as they relate to the CRS strategic plan, develop specific tactics to achieve the Society's goals, and identify potential leaders for the future. This meeting will also allow committee chairs to collaborate and work with staff to develop goals and ultimately shape CRS's future.

All of this brings to mind the idea (attributed to an African proverb) that it takes a village to raise a child. In other words, great deeds, like raising a child, are not accomplished alone. The CRS village is a large one. In fact, it is worldwide. It is not one person's vision that drives us, but the very act of working together associatively and collaboratively that makes us the professional Society that we are.

Sometimes overlooked, however, are members of our village from the CRS headquarters. Until I visited CRS headquarters, I had no idea that more than 30 professionals skilled in all aspects of association management are as strongly focused on the CRS vision and goals as we are. As partners, they play a vital role in researching, reporting, and, ultimately, implementing our initiatives. They work with every committee; they participate in every meeting. We rely on staff to see our vision and to then help make it a reality. Sharing a village and a vision, I would like to express my thanks to our partners at CRS headquarters. I cannot express how grateful I am to our staff. We are truly blessed to have this fantastic group of professionals working with us. As volunteers we could never get through all the work we need to do to make our organization run smoothly without such a wonderful staff.

I would like to take this opportunity to praise one of our key staff members, Ronda Thompson, who, unfortunately, left our organization last year. Ronda dedicated almost a decade of her working life to the efficient running of our Society. Ronda's dedication and service during her tenure acted as the cement holding the CRS family together. Ronda is a fantastic people person and made all us feel welcome and happy to be involved in CRS. Ronda's contribution to the development of today's CRS cannot be overstated. She showed incredible care for and focus on the future sustainability of CRS. Charles Dickens' statement "Do all the good you can, and make as little fuss about it as possible," sums up her personal philosophy on life. Ronda contributed quietly, behind the scenes, with an inimitable style. At the CRS Annual Meeting she exhibited an outgoing, friendly personality that, through its apparent casualness, made every member feel important and welcome. To members who volunteered their time to serve on committees, Ronda rewarded their interest and commitment with a conscientious and efficient professional working relationship. Her motto must have been "Be dedicated to the fulfillment of everyone needs." She rarely missed completing a task (no matter how large); a question to Ronda was a question answered. At the CRS Annual Meeting she knew most members and exhibitors by their first name, took the trouble to find out at least one personal detail about everybody she met, knew their research area and affiliation, and, at the drop of a hat, was able to recall these facts effortlessly to engage in conversation and make everyone feel welcome and valued. I am certain that I am speaking for our entire CRS family when I wish Ronda well in all future endeavors. We will always remember Ronda's dedication and hard work, and we will miss her dearly.

The upcoming meeting at CRS headquarters is an opportunity for us to take stock of the many assets we have as a Society—both human and financial. As CRS leaders, these meetings make it possible for us to ensure that we are not only investing our assets wisely, but that we are bringing the wisdom of our entire CRS village to bear in nurturing our growing and vibrant Society.

Working together, we will make it happen!

Diane J. Burgess ■

Interview with Dr. Jindrich Kopecek

Brian Kilfoyle and Bozena Michniak-Kohn, Ph.D.
Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, Piscataway, NJ, U.S.A.

Dr. Jindrich Kopecek is a true pioneer in the field of drug delivery. Over the years, he and his group have made considerable contributions to the field, including his groundbreaking work with hydrogels and polymer-drug conjugates. Dr. Kopecek has spent almost 50 years dedicated to his research, and he is currently celebrating his 70th birthday.

Dr. Kopecek received his M.S. degree in macromolecular chemistry from the Institute of Chemical Technology in Prague, Czechoslovakia (1961); his Ph.D. degree in macromolecular chemistry from the Institute of Macromolecular Chemistry at the Czechoslovak Academy of Sciences in Prague, Czechoslovakia (1965); and his D.Sc. degree in chemistry from the Czechoslovak Academy of Sciences in Prague, Czechoslovakia (1990). He was a postdoctoral fellow at the National Research Council of Canada in the Division of Applied Chemistry in Ottawa, Ontario (1967–1968).

Dr. Kopecek worked at the Institute of Macromolecular Chemistry at the Czechoslovak Academy of Sciences in Prague for much of his early career as a research scientific officer (1965–1967; 1968–1972), the head of the Laboratory of Medical Polymers (1972–1980), and the head of the Laboratory of Biodegradable Polymers (1980–1988). During this time, he was also a member of the Committee on New Polymers for the Ministry of Health in Czechoslovakia (1976–1986). In 1986, Dr. Kopecek moved to the University of Utah, where he has held the positions of co-director of the Center for Controlled Chemical Delivery (1986–present), adjunct professor of materials science and engineering (1987–present), professor of bioengineering and of pharmaceutics and pharmaceutical chemistry (1989–2002), chair of the Department of Pharmaceutics and Pharmaceutical Chemistry (1999–2004), and distinguished professor of bioengineering and of pharmaceutics and pharmaceutical chemistry (2002–present). During his career, Dr. Kopecek has also been a visiting professor at the Université Paris-Nord (1983, 2000), the University of Utah (1986–1988), the Academy of Sciences of the Czech Republic (1995), and Tokyo Women's Medical University (2000).

Over the course of his long and prestigious career, Dr. Kopecek has received many awards and accolades. The list is far too extensive for publication, but a few selected awards will be highlighted. Dr. Kopecek has been honored with the Presidia of the Czechoslovak and USSR Academies of Sciences (1977), the Clemson Award for Basic Research from the Society for Biomaterials and Clemson University (1995), the Founders Award from the Controlled Release Society (1999), the Millennial Pharmaceutical Scientist Award from the Millennial World Congress of Pharmaceutical Sciences (2000), the Paul Dawson Biotechnology Award from the American Association of Colleges of Pharmacy (2001), the Heyrovský Medal from the Academy of Sciences of the Czech Republic (2003), the Distinguished International Scientist Award from the Japanese Biomaterials Society (2006), and a Honorary Professorship from Sichuan University in China (2007).

Dr. Kopecek with his current research group.

Additionally, Dr. Kopecek is an AAPS Fellow (1994), AIMBE Fellow (1995), and honorary member of the Czech Learned Society (1998). He has been very active within the Controlled Release Society as a member of the Board of Governors (1988–1991), vice president (1993–1994), president-elect (1994–1995), and president (1995–1996). He has been the chair of many major conferences and study sections, including the NIH Biomaterials and Biointerfaces Study Section (2003–2006) and the Gordon Research Conference on Drug Carriers in Medicine and Biology (2004). In 2009, Dr. Kopecek provided the plenary lecture for the 36th CRS Annual Meeting in Copenhagen. He has served on the editorial boards of numerous international scientific journals in the fields of polymer chemistry, drug delivery, and biomaterials during his career and currently sits on the editorial boards of 14 journals. Dr. Kopecek's publications have been cited over 11,000 times and his Hirsch factor is 56.

With Dr. Kopecek's upcoming 70th birthday celebration in mind, we reached out to a handful of his former and current colleagues to help us paint a more vivid picture of his personality and his impact on the field of drug delivery. Dr. Kopecek is, as you will see in the following interview, very modest about his accomplishments, but his friends and colleagues are more than happy to put his phenomenal research in its proper context.

Dr. Hamid Ghandehari was a graduate student of Dr. Kopecek in the early 1990s and is currently a coworker of Dr. Kopecek in

the departments of Pharmaceutics and Bioengineering at the University of Utah. He shared with us that Dr. Kopecek "set the bar high when I was his student, and his enthusiasm was contagious. He introduced me to this whole new area of drug delivery science not to mention to camaraderie with colleagues internationally in the field. He continues to this day to have a profound impact on my career. Keys to his success are enthusiasm and love of science, hard work, innovativeness, and the ability to work with and understand people from different backgrounds."

Dr. Karel Ulbrich of the Institute of Macromolecular Chemistry at the Academy of Sciences of the Czech Republic began his career as a student of Dr. Kopecek and has continued working with him even after Dr. Kopecek moved to the University of Utah. He states that Dr. Kopecek "is one of the pioneers working in development of biomedicinal polymers, starting with hydrogel implants for surgery applications, through systematic study and design of new polymer-drug conjugates up to achievements in gene delivery research. He invented poly(HPMA) as blood plasma expander (in early seventies) and later on HPMA copolymers as efficient drug carriers. He was a key person in a group which developed the first clinically tested polymeric cancerostatics (PK1 and PK2) and later on he designed, synthesized, and studied properties of the whole range of new drug delivery systems. In addition to this he has educated a considerable number of excellent scientists working in the field of drug delivery. In my opinion his success is based on his high orderliness, full assignment, self-discipline, and personal art of stimulation of co-workers for his ideas and purposeful research. As my first teacher he introduced me to science; he showed me its beauty and with his personal example he showed me the way to carry out systematic research. I am very indebted to him for everything I learned from him during years we worked together."

Dr. Sung Wan Kim, a colleague of Dr. Kopecek at the University of Utah, says that "Henry has shown time and again that he is the true pioneer in drug targeting research. He has done great work in hydrogels. Henry pioneered it, and there are hundreds of publications in this area, of which most of them reference his work. Henry is a very nice, charming, and warm person. I expect to see him continue to do his best research in the future."

Dr. Allan S. Hoffman of the University of Washington in Seattle, first met Dr. Kopecek in the 1960s at MIT in Cambridge, MA. The two had mutual research interests and developed a friendship that has lasted since. In Dr. Hoffman's words, "over the years, Jindra has been a good friend and a very inspiring colleague. He is a role model for all of us as he continues to produce innovative and scholarly work and to share it in his modest and honest way. This has immensely inspired me. He is one of the most admired scientists in the drug delivery field, with many awards to his credit, and still he remains modest, friendly, and open to us all."

When further asked about Dr. Kopecek's impact on the field of drug delivery, Dr. Hoffman replied, "I think that Jindra Kopecek is one of the most outstanding drug delivery researchers in the world. His work exemplifies an exciting and powerful combination of creative and visionary thinking and superb experimentation. Jindra was one of the very first pioneers in polymer-drug conjugates. In 1975 a US patent was issued to him and his group at the Institute of Macromolecular Chemistry in Prague on a new drug carrier composition: they had conjugated an anti-cancer drug to the backbone of a newly synthesized polymer, poly(hydroxypropyl methacrylamide) or PHPMA, via an enzyme-degradable peptide spacer. It is worth noting that this concept was patented by Kopecek et al. before anything had been published on PEGylation of drugs. This work led to the clinical application of the PHPMA-doxorubicin conjugates, which was the result of a collaboration of Kopecek and his group in Prague with Ruth Duncan and her colleagues in the UK.

Jindra has continued to make major contributions to the field of drug delivery ever since then, but it's that early pioneering work that stands out in my mind as one of the best examples of his innovative and visionary thinking, and the resultant impact that it has had on our drug delivery field."

When asked what makes Dr. Kopecek successful, Dr. Hoffman replied, "in my opinion it's a combination of his original thinking, meticulous experimentation, lucid communication of results, willingness to share ideas openly and honestly with colleagues, and warm and friendly attitude…all in all, a brilliant guy with a sweet and gentle personality. Now that's a dynamite combination!"

We would like to sincerely thank Dr. Kopecek for conducting this interview with us, and we would like to wish him a very happy 70th birthday. To mirror the sentiment of his colleagues, we would like to acknowledge all of the great research that Dr. Kopecek and his group have provided to this point, and we look forward to all of their future contributions.

Interview

Q ***Before enrolling in university, what influenced you to pursue a career in science? What other fields interested you? How were the sciences structured in Czechoslovakia in the 1960s?***

A At high school I was interested in chemistry and mining engineering (I grew up in a mining area); finally, chemistry appeared more interesting, so I applied to the Prague Institute of Chemical Technology (a well-known alumnus was Vladimir Prelog, the Nobel laureate) and succeeded to be admitted to the macromolecular chemistry program. For graduate school, I chose the Institute of Macromolecular Chemistry of the Czechoslovak Academy of Sciences. In Czechoslovakia, as in many East European countries, the Academy of Sciences was the most supported research institution. Its structure was something between a (US) National Laboratory and a graduate school. When I became independent as laboratory head in 1972, the majority of my coworkers were scientists; graduate students were a minority.

Interview with Dr. Jindrich Kopecek continued on page 6

Interview with Dr. Jindrich Kopecek continued from page 5

Q ***When you graduated from the Institute of Macromolecular Chemistry at the Czechoslovak Academy of Sciences in Prague, what factors played a role in your decision to stay in academia?***

A At that time, the level of research in the Czechoslovak chemical industry was not very high. On the other hand, the research in the Institute of Macromolecular Chemistry was exciting. It was one of the leading centers of macromolecular chemistry research worldwide. My mentor Dr. Drahoslav Lím invented hydrogels, the first rationally designed biomedical polymers. The head of the institute Prof. Otto Wichterle invented (hydrogel-based) soft contact lenses. They sold the license to the National Patent Development Corporation, who sublicensed it to Bausch and Lomb; this was the start of the soft contact lens industry in the USA. It was a unique environment for a curious young scientist.

Q ***Could you walk us through the steps you took in your career that brought you to the University of Utah?***

A My mentor Dr. Lím was a visiting professor at the University of Utah in 1969; that established the contact between Prague and Salt Lake City. I was offered a position in Utah in 1979, but first hesitated to move. I accepted a visiting professorship in 1983, but it took 3 years to clear the red tape, and I came to Utah in 1986. I received my first NIH RO1 grant when I was still a visiting professor on a J-1 visa. That convinced me that I can raise funds to support a research group at Utah and decided to move.

Q ***What do you regard as the most significant achievement(s) of your scientific career thus far?***

A On an educational level, I am happy that many of my students seem to love science and are successful in academia and industry. On a scientific level: a) Hydrogels developed in my Prague laboratory were translated into the clinic (J. Biomed. Mater. Res. 9: 675-685, 1975); b) My laboratory contributed considerably to the development of water soluble-polymer–drug conjugates (Adv. Drug Delivery Rev. 62: 122-149, 2010); c) The conception of hybrid self-assembling hydrogels based on coiled-coil recognition (Nature 397: 417-420, 1999; Biomacromolecules 7: 1187-1195, 2006); d) Finally, we have demonstrated that principles of biorecognition that we have learned in designing new biomaterials can be used to design new drug-free macromolecular therapeutics (Ang. Chem. Int. Ed. 49: 1451-1455, 2010).

Q ***What are the current research interests of your group?***

A My laboratory has projects in the design of new nanomedicines for the treatment of ovarian and prostate cancer and treatment of osteoporosis. In the biomaterials area we study hybrid hydrogels, whose self-assembly from graft and block copolymers is mediated by coiled-coil and β-sheet formation. Recently, we have designed a new paradigm in drug delivery—drug-free macromolecular therapeutics: apoptosis in B cells can be initiated by crosslinking of CD20 receptors mediated by coiled-coil formation at cell surface.

Q ***How have your research interests changed over time? Have these changes been impacted by changes in the field in general?***

A My interests gradually evolved from pure chemistry to an interdisciplinary field comprising pharmaceutical chemistry, biomaterials, bioengineering, and drug delivery. First, I became interested in the biocompatibility of hydrogels of different chemical and physical structures. When hydrogels we studied and developed were successfully used in the clinic, I focused my attention on the biocompatibility of water-soluble polymers and their potential as drug carriers. The effort to understand the mechanism of action of polymer-drug conjugates forced us to study molecular biology, which helped us to design and synthesize genetically engineered polymers and self-assembling hybrid copolymers. It was a gradual, logical development of ideas.

Q ***Recently your group has focused on: a) polymeric nanomedicines for the treatment of ovarian cancer, b) polymeric nanomedicines for the treatment of prostate cancer, c) polymeric nanomedicines for the treatment of musculoskeletal diseases, and d) smart biomaterials prepared by self-assembly of block and graft copolymers. Could you briefly discuss each and possibly provide a reference for our readers?***

A In the area of ovarian cancer we focus on the subcellular targeting of drugs. The possibility to direct the fate of the drug on the subcellular level has the potential to enhance efficacy (Mol. Pharmaceutics 5: 776-786, 2008); in the area of prostate cancer we study double targeted conjugates and mechanism of their internalization and action (J. Controlled Rel., 2010; doi: 10.1016/j.jconrel.2009.12.022); in the area of musculoskeletal diseases we have designed bone targeting conjugates that enhance bone formation after administering one dose to ovariectomized rats (Pharmaceutical Res. 25: 2889-2895, 2008). Moreover, bone targeted combination conjugates containing polymer-bound angiogenesis inhibitors target bone metastases and calcified neoplasms (PLoS ONE 4(4) e5233 (2009); doi:10.1371/journal.pone.0005233). In the area of smart biomaterials we designed hydrogels crosslinked with an adenylate kinase triple mutant; these hydrogels convert substrate recognition mediated nanoscale conformational changes into macroscopic motion (J. Am. Chem. Soc. 130: 15761-15762, 2008). In addition, we designed a pair of oppositely charged peptides that formed antiparallel coiled-coil heterodimers and served as crosslinkers during self-assembly of hybrid graft copolymers (Biomacromolecules 7: 1187-1195, 2006). Extending this biorecognition concept onto a biological system, we have designed an apoptosis induction system based on the biorecognition of coiled-coil forming peptides at the cell surface (Ang. Chem. Int. Ed. 49: 1451-1455, 2010).

Q ***Could you briefly describe the role of controlled release in your work?***

A Controlled release is one of the major design principles of the majority of our projects.

Q ***As a former president, member of the Board of Governors, and longtime member of the Controlled Release Society, what role(s) do you think the Society has played? What role should it play going forward?***

A The Society had a decisive impact on the growth of research in the area of drug delivery worldwide. Its main focus in the past was on basic science, presentation of new ideas, and their translation into the clinic. I think that it is important that the Society maintains and enhances the focus on and support of innovative research, which is the way to attract outstanding graduate students with different scientific backgrounds to actively participate in the Society and develop into future Society leaders.

Q ***What scientists have played an important role in your scientific development? Are there collaborators you've worked with that you would like to recognize?***

A There were several important points in my career. First, I was lucky to be assigned into a great research group for my graduate studies—in those days the mentor was assigned, not chosen. Second, I was fortunate to have outstanding coworkers and graduate students both in Prague and in Utah, including my wife Pavla (we have been working together for more than 30 years). Third, my early collaboration with Drs. John Lloyd, Ruth Duncan, and Blanka Říhová helped to broaden my biological background. Last, but not least, my move to the University of Utah in the mid-1980s. The interdisciplinary research atmosphere stimulated me to move to new research areas—the mechanism of action of macromolecular therapeutics, the development of genetically engineered and self-assembling biomaterials, and, recently, the design of drug-free macromolecular therapeutics. My present laboratory is composed of excellent graduate students and outstanding senior coworkers: Pavla Kopečková (research professor), Jiyuan Yang (research associate professor), Jihua Liu (research assistant professor), and Huaizhong Pan (research associate). Their support is significant in keeping me fully active—4 new Ph.D. students and 1 postdoctoral fellow joined our lab this academic year.

Q ***If you were to give advice to a recent or soon-to-be graduate, what would it be?***

A The most important point is to choose a career that will make you happy for many years to come. Since I do not have experience in industry, my advice is more directed to students going to academia, but the major points are generally valid: Work hard. Do not just modify the research aims of your mentors, but formulate your own research area. Remember that the future of science in general, and drug delivery in particular, is in the interdisciplinary approach to hypothesis formulation and problem solving. Choose an interdisciplinary topic that is important, fun, challenging, but doable. Move beyond boundaries. Generally, the most important attributes for a successful career are persistence; curiosity; good analytical skills; inventiveness; communication skills; eagerness to learn new things; ability to accept advice; not to change after success; and leading by example, not by force.

Dr. Kopecek's research group skiing.

Q ***It's now been over 50 years since you started pursuing your M.S. in macromolecular chemistry from the Institute of Chemical Technology in Prague. Has the time gone by fast? Have your experiences surpassed your initial expectations? What lessons have the 50 years in science taught you that you could share with us?***

A When I finished my Ph.D. at the age of 25, I decided to work hard for 5 years and then evaluate if I chose the right career. After 5 years, I did not lose time thinking of my initial milestone. I liked the work and did not plan to do anything else.

Q ***What would you select as the most important seminal highlight in your career?***

A I think that the most important highlight is the fact that I love to go to work every day after 50 years in science. No awards or formal recognition can compete.

Q ***Which one of your many discoveries, would you say, influenced the scientific field most?***

A Based on the number of publications from other laboratories, it is the design and development of HPMA [*N*-(2-hydroxypropyl)methacrylamide] copolymers as drug carriers.

Q ***What personal attributes have allowed you to be so successful in your scientific career?***

A I like my work, and I work hard; after 50 years of research, I am still excited when my students present me with new data.

Q ***Motivation is an important characteristic of a successful person (regardless of their chosen field). What has motivated you to work so hard for so long?***

A The most rewarding aspect of academic life is to witness the development of students into great scientists and colleagues.

Q ***Outside of your scientific endeavors what hobbies do you enjoy (follow-up questions will potentially come from this one)?***

A I follow international relations, collect stamps, and like skiing.

Q ***What is your favorite skiing area?***

A My favorite skiing area in Utah is Alta. Utah has really "the best snow on earth." The quality of snow is amazing. ■

Register to Attend One of These Educational Workshops in Portland!

The following workshops will be offered at the 37th Annual Meeting & Exposition of the Controlled Release Society in Portland, OR. All three educational workshops will be held on Saturday, July 10, at the Oregon Convention Center. Separate registration is required for educational workshops. Register today for the educational workshop that is of interest to you.

Educational Workshop 1: Nanomedicine: From Materials Design to Clinical Applications
Chaired by Hamid Ghandehari, University of Utah, U.S.A., and Claus-Michael Lehr, Saarland University, Germany

During this workshop the attendees will learn and engage in a discussion of concepts related to the design and synthesis/fabrication of nanomaterials, their interaction with cells and biological systems, and their translation to the clinic.

Nanoengineered Particles for Therapeutic Delivery, **Frank Caruso,** University of Melbourne, Australia
Nanoparticle Interactions with the Bio-interface, **Ken Dawson,** University College Dublin, Ireland
Nanostructured Interfaces for Therapeutic Delivery, **Tejal Desai,** University of California-San Francisco, U.S.A.
Architectural Influence of Nanoconstructs on Toxicity, Cellular Uptake, and Biological Fate, **Hamid Ghandehari,** University of Utah, U.S.A.
Polymer Nanomaterials for Drug Delivery, **Alexander Kabanov,** University of Nebraska Medical Center, U.S.A.
Nanomedicine for Targeting Epithelial Barriers: Intestines, Skin, and Lung, **Claus-Michael Lehr,** Saarland University, Germany
Interactions of Nanoparticles with Cells and Tissues: Role of Asymmetry, **Samir Mitragotri,** University of California-Santa Barbara, U.S.A.
Healing the Hearing with Targeted Delivery, **Ilmari Pyykkö,** Tampere University Hospital, Finland

Educational Workshop 2: Characterization of Nanoparticles and Microparticles Using State-of-the-Art Techniques
Chaired by Zhibing Zhang, University of Birmingham, U.K., and Nicole Papen-Botterhuis, TNO Science & Industry, The Netherlands

This workshop will provide knowledge on the possibilities of many state-of-the-art techniques used to characterize encapsulates for various controlled release applications, such as (cryo)electron microscopy (SEM/TEM), dynamic light scattering (DLS), zeta potential measurements, dissolution testing (DSP), atomic force microscopy and micromanipulation, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), dynamic *in vitro* gastrointestinal models (TIM), confocal laser scanning microscopy (CLSM), *in vivo* toxicology studies of nanoparticles, permeation measurements for determining barrier properties, etc. After this workshop, you will be able to decide which characterization tool gives you the best answer to your problem.

Characterization of Polymeric Materials Using DSC, X-Ray Diffraction (XRD), and Nuclear Magnetic Resonance (NMR), **Finizia Auriemma,** University of Naples Federico II, Italy
Determination of the Mechanical Strength of Microcapsules by Micromanipulation and the AFM, **Zhibing Zhang,** University of Birmingham, U.K.
Electron Microscopy Techniques for Micro- and Nano-particle Analysis, **Wim Busing,** FEI Company, The Netherlands
Overview of Existing Characterization Techniques Used in the Pharma Industry, **Samir Haddouchi,** SPS Pharma Services, France

Studies on Coated and Encapsulated Components with Dynamic Gastrointestinal Models, **Rob Havenaar,** TNO Quality of Life, The Netherlands
Aspects of Characterization and Toxicology of Nanoparticles, **Nancy Monteiro-Riviere,** North Carolina University, U.S.A.
Light Scattering Techniques for the Measurement of Size and Zeta Potential of Nanoparticles, **Ulf Nobbmann,** Malvern, U.S.A.
Fundamentals of Permeation and Applications in Materials Design of Controlled Release Systems, **James Paik,** Kalsec Inc., U.S.A.
Introduction to Characterization of Nanoparticles and Microparticles Using State-of-the-Art Techniques, **Nicole Papen-Botterhuis,** TNO Science & Industry, The Netherlands
Methods Based on Confocal Laser Scanning Microscopy in the Characterization of Microcapsules, **Dominic Rochefort,** University of Montréal, Canada

Educational Workshop 3: Enhancing Bioavailability of Poorly Soluble Drugs via Melt Extrusion Technology: From Formulation to Commercialization
Chaired by Nigel Langley, BASF, U.S.A., and Michael Repka, University of Mississippi, U.S.A.

The workshop's primary goal is to provide updates to existing knowledge of hot-melt extrusion (HME) such that attendees will increase their expertise with respect to this rapidly emerging processing technique. The workshop will also present an overview for those who are new to the technology such that these scientists may examine the opportunities available via HME. Attendees will also hear about the outlook regarding further perspectives for this technology.

Solubility and Other Physicochemical Considerations for Delivery of Bioactives: The Hot-Melt Extrusion Alternative, **Fernando Alvarez,** Amgen, U.S.A.
Successful Commercialization of Melt-extruded Bioactives, **Joerg Breitenbach,** Soliqs-Abbott GmbH & Co. KG, Germany
Controlled Release Systems Produced by HME, **Tom Durig,** Ashland/Aqualon, U.S.A.
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Design of Stable Extruded Solid Dispersions, **Craig McKelvey,** Merck, U.S.A.
Melt Extrusion: Case Studies of Drug Delivery Systems, **Dave A. Miller,** Roche Pharmaceuticals, U.S.A.
Melt Extrusion of Poorly Soluble Bioactives: Formulation and Processing, **Feng Zhang,** PharmaForm, LLC, U.S.A.

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Spotlight on the
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Portland, Oregon, U.S.A.

Portland is the gateway to an outdoor enthusiast's playground…

- A leisurely drive west of Portland, you'll find the scenic Columbia River Gorge—a perfect get-away for a day or two. Follow in the footsteps of Lewis and Clark as you search out the more than 70 waterfalls (the most famous being Multnomah Falls), numerous hiking trails, Bonneville Lock and Dam (salmon and sturgeon viewing area), world-class windsurfing at Hood River, historic inns, and interesting museums such as Vista House, the International Museum of Carousel Art, and the Maryhill Museum of Art.
- No visit to Oregon is complete without a trip to the Oregon coast. Less than one hour from Portland, Oregon's 400 miles of rugged coastline is dotted with scenic fishing villages, artist communities, exclusive golf resorts, secluded coves, tide pools teeming with aquatic plants and sea life, miles of pristine sandy beaches, and the Sea Lion Caves (the largest sea cave in the world and permanent home to more than 200 Stellar sea lions).
- Less than two hours west of Portland, you'll find majestic Mt. Hood and the historic Timberline Lodge. Palmer Glacier is the only glacier in North America where you can ski and snowboard year-round.

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Columbia River Gorge and Vista House by Larry Gedis, courtesy of Travel Oregon.

37th Annual Meeting & Exposition of the Controlled Release Society

CRS Innovation Sunday—NEW!

Science • Partnering • Commercialization

Sunday, July 11, 2010

Come be part of CRS Innovation Sunday and build your networks for success.

Partnering, technology, innovation, big pharma, entrepreneurs, research, commercialization—you will find all of these elements in the fast-paced programming focused on taking innovative science into the commercial sector. Who will come to Sunday's programming? People with good ideas, people who need good ideas, people who want to commercialize good ideas! Highlights of Innovation Sunday's programming are listed below.

One-on-One Partnering

The CRS Annual Meeting & Exposition has long been known as an exceptional venue to network with legends and innovative newcomers in the field of controlled release and drug delivery. To further help you find just the right contact for your project, product, or innovative idea, CRS will offer formal one-on-one partnering opportunities. Watch the CRS website for further details.

Open Forum: From Bench to Market—The Route to Commercial Success

CRS Innovation Sunday is delighted to have the inside story from entrepreneurs and large pharma in two sessions with open forum discussions.

Converting Innovation into Commercial Success
Hear from and discuss with entrepreneurs as they give their practical insight on how to take innovation and build it into a commercial venture.

Current Industry Needs in Drug Delivery Partnerships
Big pharma panelists share their strategic plans for current and future drug delivery. It is the opportunity to directly ask what they are looking for in an alliance or partnership.

State of the Industry Keynote

Returning by popular demand, DataMonitor President Sarah Terry will present the latest statistics, trends, and drivers of the industry along with the projected future of drug delivery.

Releasing Technology Workshops

Hosted by individual companies, these workshops focus on in-depth facets of products and services supporting research and development in controlled release technologies.

Soapbox Sessions

The Soapbox Sessions introduce the latest, most novel technologies, products, and services for delivery in bioactive materials, consumer and diversified products, and animal health. Identify potential collaborations in these fast-paced presentations and during the one-on-one sessions following the presentations.

Exposition Grand Opening and Welcome Reception

CRS Innovation Sunday culminates in the Exposition Hall with the opening of the exposition and a welcome reception. Join 100+ companies and more than 1,500 attendees where thousands of products, services, and innovations still to be developed can be discussed one-on-one. Also the site for posters, come to the Exposition Hall for discovery, solutions, and opportunities.

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A Synthetic Mycobacterial Monomycoloyl Glycerol Analogue Stabilizes DDA Liposomes

Pernille Nordly,[1,2] Esra Alici Pedersen,[1] Tayba Sajid Khilji,[1] Else Marie Agger,[2] Lene Jørgensen,[1] Hanne Mørck Nielsen,[1] Karen Smith Korsholm,[2] Henrik Franzyk,[3] and Camilla Foged[1]

Mycobacterium species, including *Mycobacterium tuberculosis*, constitute some of the most immunostimulatory microorganisms. Several compounds from the mycobacterial cell wall, including lipids, are involved in host cell activation. The mycobacterial glycolipid monomycoloyl glycerol (MMG) has been extracted from *Mycobacterium bovis* (bacillus Calmette-Guérin) and was found to be a potent stimulator of the immune system (1). A synthetic analogue based on 32 carbon atoms (Figure 1) exhibited comparable immunostimulatory activity. In combination with cationic liposomes based on dimethyldioctadecylammonium (DDA) (Figure 1), MMG induced significant levels of interferon-γ after immunization of mice with the adjuvant and Ag85B-ESAT-6 antigen (1) and induced protective immunity in tuberculosis challenge experiments (2).

The use of synthetic analogues of mycobacterial lipids in combination with cationic liposomes as vaccine adjuvants provides a promising strategy for exploiting the immunostimulatory activity of mycobacterial cell wall components but without associated toxicity issues. As the immunostimulatory effect of DDA/MMG liposomes has been demonstrated (1,2), the objective of the current study was to characterize the physico-chemical properties of DDA/MMG liposomes. Thus, we resynthesized MMG based on 32 carbon atoms, and DDA/MMG liposomes were prepared using the thin film method, as previously described (3). Incorporation of MMG in DDA liposomes resulted in liposomes with a polydisperse size distribution, with an average particle size of approximately 600 nm. The surface charge of the vesicles was not affected by the inclusion of MMG due to its lack of ionizable functionalities. The gel-to-liquid phase-transition temperature of undiluted vesicles in suspension was determined using differential scanning calorimetry. Incorporation of MMG decreased the phase-transition temperature and broadened the phase-transition peak (Figure 2), indicating that a phase-separation phenomenon, such as formation of local ordered DDA and/or MMG microdomains, took place.

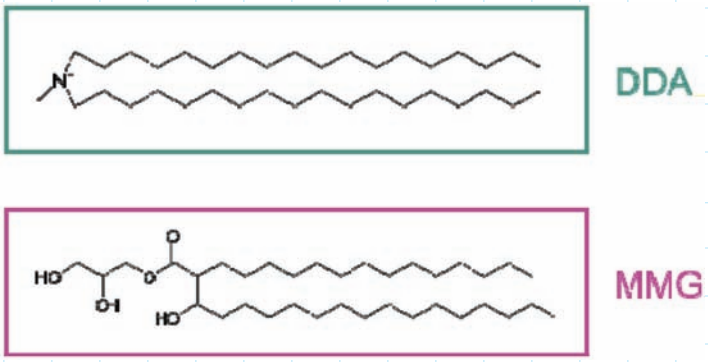

Figure 1. *Chemical structure of dimethyldioctadecylammonium (DDA) and monomycoloyl glycerol (MMG).*

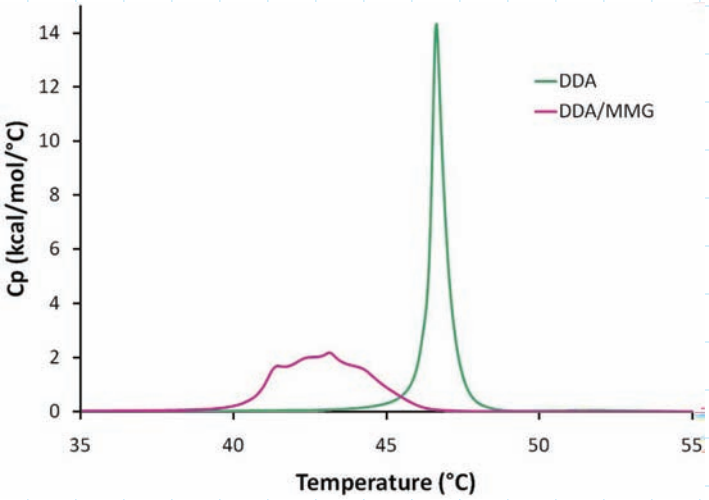

Figure 2. *Thermograms of DDA and DDA/MMG vesicles measured by differential scanning calorimetry.*

It has previously been reported that DDA liposomes are unstable in suspension (3), and therefore, we investigated whether MMG provides a stabilizing effect on DDA liposomes. Evaluation of the stability of DDA/MMG liposomes indicates that MMG stabilizes these liposomes, since their average particle size remained almost constant over time at 4°C (Figure 3), whereas DDA liposomes without MMG aggregated after a few weeks, as previously observed (3). This stabilization of the otherwise unstable DDA liposomes may be attributed to increased hydration of the lipid membrane, and to corroborate this hypothesis, surface pressure/area isotherms of monolayers of DDA and DDA/MMG were obtained using the Langmuir-Blodgett technique.

The Langmuir-Blodgett technique (Figure 4) is a sensitive tool for investigating interactions at water-lipid interfaces and, thus,

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3 University of Copenhagen, The Faculty of Pharmaceutical Sciences, Department of Medicinal Chemistry, Copenhagen, Denmark.

may be used to evaluate the surface pressure of a lipid monolayer under such conditions (Figure 5). A very low surface pressure is obtained when the lipids are dispersed on the aqueous subphase and, hence, do not interact with one another (gas phase). When the monolayer is subjected to continuous compression, the hydrophobic lipid tails begin to interact, and the surface pressure increases (liquid-expanded phase). As the lipid tails are forced into closer contact, they are oriented more vertically into the air phase, and a phase transition may be observed. Further compression of the monolayer results in increased surface pressure as the lipid tails, as well as the polar head groups, interact (liquid-condensed phase). If the tails are aligned vertically into the air phase and compression is continued further, the surface pressure increases dramatically (solid phase) until the monolayer collapses (collapse point).

The results indicate that incorporation of MMG allows for higher surface pressure of DDA monolayers at the collapse point (Figure 6), suggesting that the glycerol head group of MMG stabilizes the water-lipid interface. Also, inclusion of MMG appears to provide a more tightly packed lipid monolayer, as the molecular area was decreased compared with pure DDA at a given surface pressure. This suggests that the presence of MMG relieves the repulsion between the positively charged ammonium head groups of the DDA molecules. Increased stability of DDA/

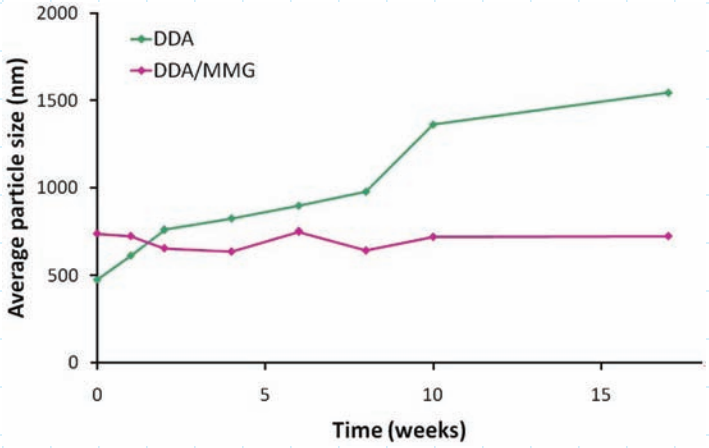

Figure 3. *Stability of DDA and DDA/MMG vesicles during storage at 4°C.*

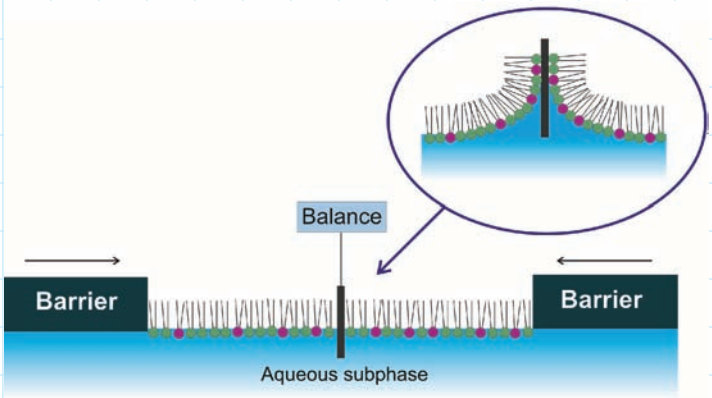

Figure 4. *Schematic illustration of the principle of the Langmuir-Blodgett technique.*

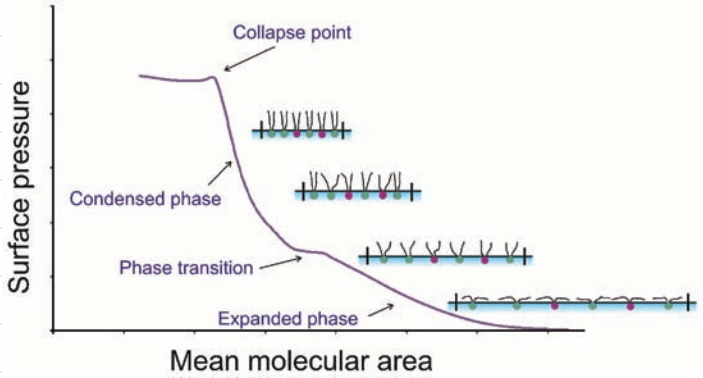

Figure 5. *Example of a Langmuir-Blodgett surface pressure/area isotherm of a lipid monolayer.*

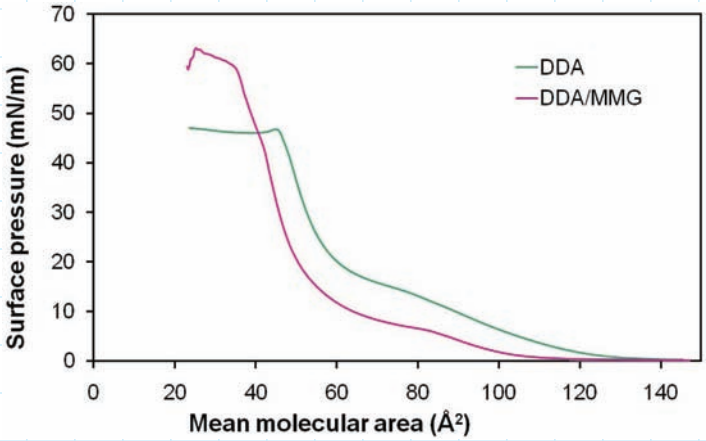

Figure 6. *Langmuir-Blodgett surface pressure/area isotherms of DDA and DDA/MMG monolayers.*

MMG liposomes, thus, can be attributed to 1) a higher degree of hydration of the lipid membrane, since the glycerol head groups interact with water; and 2) decreased intermolecular repulsion between DDA head groups. Similarly increased hydration has been observed previously for DDA liposomes with the immunostimulatory compound trehalose-6,6-dibehenate (TDB) incorporated (4). Likewise, TDB stabilized the DDA liposomes, and it was demonstrated using the Langmuir-Blodgett technique that TDB caused increased hydration of the lipid membrane. The adjuvant formulation based on DDA/TDB liposomes, designated CAF01, is currently entering a clinical phase I trial with the tuberculosis antigen AG85B-ESAT-6 (5).

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Novel Methods for Developing Clinically Relevant Product Specifications

A workshop co-sponsored by the American Association of Pharmaceutical Scientists and the Controlled Release Society.

Saturday, November 13, 2010
Morial Convention Center
New Orleans, Louisiana, U.S.A.

To be held immediately prior to the FIP Pharmaceutical Sciences World Congress 2010 in association with the AAPS Annual Meeting.

Who should attend?

Bench and clinical scientists involved in the development or regulation of modified release formulations and the optimization of dosing strategies.

Speakers include:

Introduction and objectives. *Marilyn Martinez, FDA*
Quality by Design: Impact on drug development and its global applications. *Moheb Nasr, FDA*
Design space and product specifications: A risk assessment approach. *Raafat Fahmy, FDA*
Quality Product Target Profile: Integrating product *in vivo* performance in a patient population with product design. *Arzu Selen, FDA*
Development of oral drug delivery platforms based upon patient GI characteristics. *Kevin Johnson, Intellipharm LLC, and John Crison, Simulations Plus*
A nonlinear mixed effects IVIVC model for multi-release drug delivery systems. *Adrian Dunne, Johnson & Johnson and University College Dublin*
The use of therapeutic drug monitoring to identify the relationships between optimized dosing strategies (input function) versus patient characteristics (covariates): Using this information to develop a target for *in vivo* product release characteristics. *Roger Jelliffe, University of Southern California*
The development of mechanistic population pharmacokinetic models to support the development of targeted release characteristics from modified release dosage forms. *William Jusko, University at Buffalo*
The use of modeling and simulation to target dosing strategies and predict optimal *in vivo* product release characteristics in a pediatric population. *Jeffrey Barrett, Children's Hospital of Philadelphia*
Integrating patient *in vivo* performance characteristics into product design and specifications: a manufacturing perspective. *Maria T. Cruañes, Merck & Co., Inc.*

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Tracking the *In Vivo* Fate of High Molar Mass Poly(vinyl alcohol) Using Multispectral Fluorescence *In Vivo* Imaging

Andreas Schädlich,[1] Yanjiao Jiang,[2] Jörg Kressler,[2] and Karsten Mäder[1]
Martin Luther University Halle-Wittenberg, Halle (Saale), Germany

Introduction

Poly(vinyl alcohol) (PVA) is a nonionic, water-soluble, and biocompatible polymer (1). In the pharmaceutical industry, it is widely used for biomedical applications, such as contact lenses and scaffolds for wound healing and tissue regeneration. PVA hydrogels are also extensively studied for the controlled release of therapeutic molecules. It has also been reported that PVA membranes can be used for adhesion prevention of postsurgical abdominal adhesions (2). Adhesions are internal scars that develop after trauma and involve the injured tissue and peritoneum. An ideal barrier would be a gel or liquid solution that can injected to the place of interest. Following peritoneal healing, it should be reabsorbed and eliminated. PVA (125,000 g/mol) elimination studies in rabbits showed that PVA passes the kidneys despite its high molar mass (3).

The question is whether the elimination results can be assigned also to a high molecular weight (195,000 g/mol) PVA. The noninvasive method of optical imaging was used to measure how long the PVA is localized at the area of injection to follow possible accumulation in the body and examine whether PVA is still eliminated through the kidneys. PVA was labeled with the fluorescence dye tetramethyl-rhodamine-5-carbonyl azide (TMR) (from Invitrogen) in anhydrous dimethylsulfoxide at 80°C. The dialyzed PVA-TMR was dissolved in water (5%, wt/wt) (Figure 1).

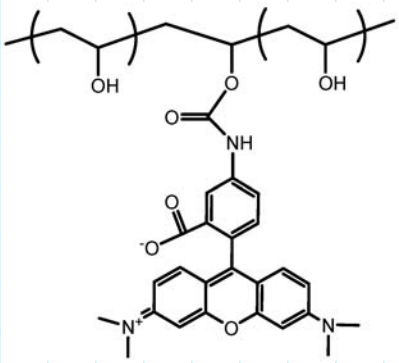

Figure 1. *Chemical structure of TMR-labeled poly(vinyl alcohol).*

Methods

In vivo imaging was performed with the Maestro™ *in vivo* imaging system (CRi, Woburn, MA). Distribution and accumulation were studied by measuring the whole body from the abdominal side at predetermined time intervals using a green filter set (580-nm long-pass emission filter). Multispectral imaging cube sets were acquired. By unmixing and further segmentation, it was possible to separate the PVA-TMR signal from the auto fluorescence signals of the mice. The total signal, as the sum of all pixel values from the extracted PVA-TMR signal, and the maximum pixel values were then calculated. Confocal microscope pictures were captured using the True Confocal Scanner SP2 fluorescence microscope (Leica Microsystems, Heidelberg, Germany). For excitation an argon laser (488 nm) was used.

Results

Using the Maestro™ software from CRi it was possible to separate the *in vivo* fluorescence PVA-TMR signal from the background signals of the mice (Figure 2). After injection of the PVA-TMR dispersions, high concentrations of labeled polymer could be detected in the area of the abdomen. From there it was distributed via the body liquids throughout the whole body (Figure 3). The circulated polymer was accumulated in the area under the skin but also in the region of the fat pad. Using the Maestro™ software it was possible to separate the accumulated PVA-TMR signals between the skin and other parts like the fat pad that were analyzed after masking the skin signal.

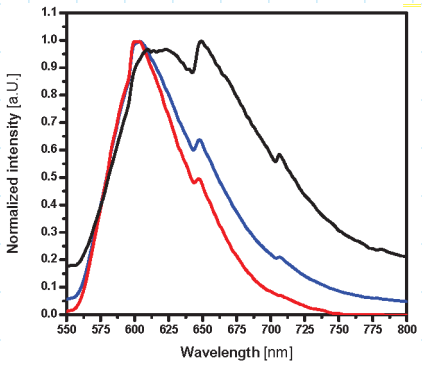

Figure 2. *Normalized emission fluorescence spectra; blue:* in vivo *extracted PVA-TMR spectra; black: background signal of an untreated mouse; red: manually computed PVA-TMR spectra.*

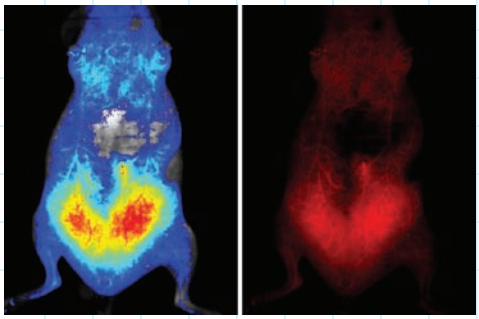

Figure 3. *Unmixed images of one nude, female mouse 24 hr after i.p. injection. The incremental jet color images represent the threshold fluorescence PVA-TMR signal. The red color indicates areas of detected PVA-TMR signal.*

The total fluorescence intensities from the abdomen site of the body increased to a maximum within the first week, which was the result of the distribution throughout the whole body. After this time, the PVA-TMR was continuously released and mainly eliminated through the kidneys (Figure 4). Surprisingly, we detected obvious differences between male and female mice in

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2 Department of Chemistry.

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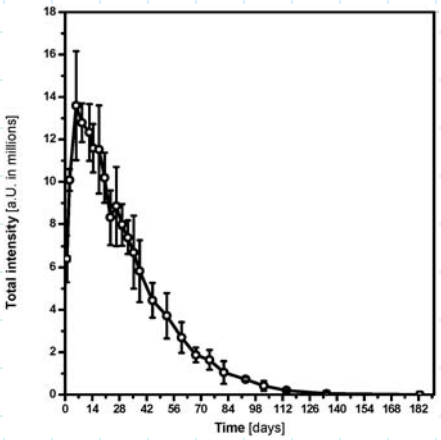

Figure 4. *Total fluorescence intensities throughout the whole body from the abdomen side of three female mice over a time period of 26 weeks after i.p. administration of the PVA-TMR dispersion.*

the region of the celiac fat (*n* = 3 of each group) (Figure 5). In female mice, PVA-TMR accumulated mainly in the abdomen area and was localized there over a time period of about 100 days. In contrast to this, the main intensities measured over nearly the same time period in male mice were found in the thigh (Figure 5).

Analyzing the maximum signal, it could be shown that this parameter remained constant during the first three weeks. Later on, the signal decreases continuously (Figure 6). The PVA-TMR was released slower compared to other tissues. This can be attributed to the poor perfusion of the fat tissue. Thus, the total fluorescence intensity was reduced faster than the maximum intensity.

The signal accumulation in the fat depot was also studied in more detail *ex vivo* using a confocal microscope. The pictures from fat cells show that PVA-TMR was accumulated in the intra-cellular region of the cells (Figure 7A and B). These results could also be confirmed with an *in vitro* experiment in which fat tissue was treated with PVA-TMR and then washed with water to check whether it was bound (Figure 7C). The experiment confirmed the expectations after *in vivo* measurements.

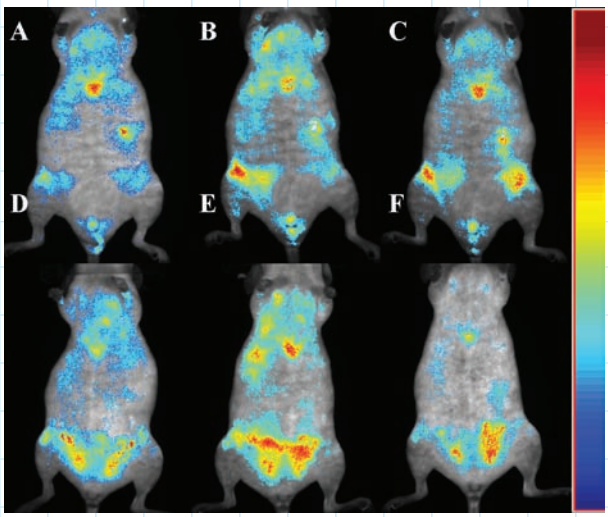

Figure 5. *Fluorescence intensity images of one male (**A–C**) and one female (**D–F**) mouse after 2 (**A** and **D**), 8 (**B** and **E**), and 30 (**C** and **F**) days. The incremental Jet color represents the threshold fluorescence TMR signal. Differences in PVA-TMR distribution are obvious. The high intensity of the spot in the chest area was identified by autopsy of three mice as an artifact caused by the xiphoid cartilage.*

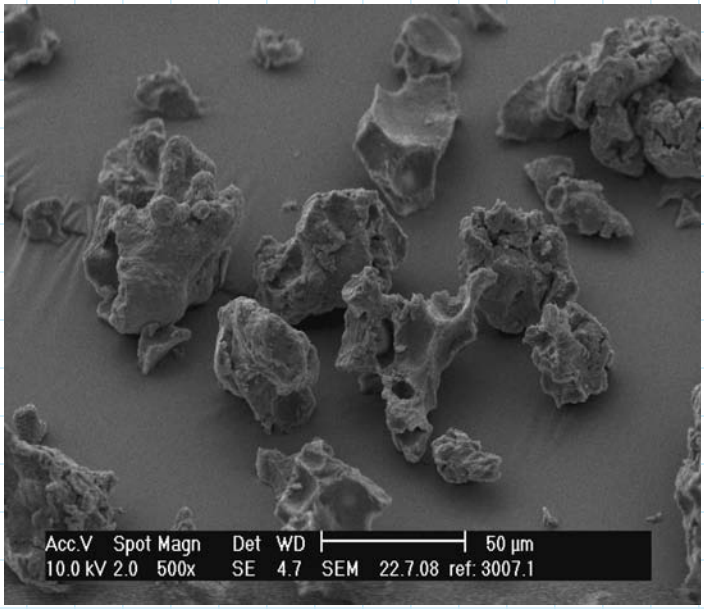

Figure 6. *Maximum intensity values of the PVA-TMR signal for 26 weeks after i.p. administration* (n = *3).*

Conclusions

The intraperitoneally administrated fluorescent-labeled PVA dispersions were successfully characterized using the Maestro™ *in vivo* imaging system. PVA was accumulated in the skin as well as in the fat tissue of mice. We detected differences between the male and female mice. PVA-TMR was slowly and continuously released over months. Despite its high molar mass, PVA-TMR was mainly eliminated with the urine. Accumulation in the liver and kidneys, as well as in feces, was not observed. However, the quantum efficiency of the TMR was not high enough to exclude it completely. Therefore, PVA was labeled with a NIR dye, and the *in vivo* experiments will start soon.

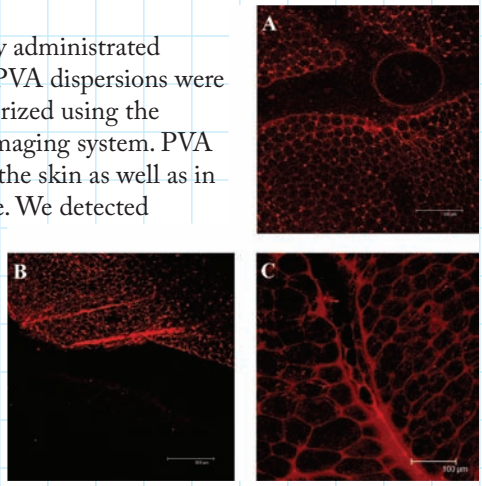

Figure 7. *Confocal microscopy images of fat tissue extracted from the abdomen; **A**, fat 180 days after i.p. injection; **B** (top), fat tissue; **B** (bottom), untreated fat; **C**,* ex vivo *PVA-TMR incorporated fat tissue.*

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Innovations in Process Technology for Producing Sub-micron Crystals of Therapeutic Agents

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Background

Recent trends in the discovery of new medical entities have shown a progressive rise in candidate drugs with sub-optimal biopharmaceutical characteristics, particularly those demonstrating low aqueous solubility (1). For many of these molecular entities, sub-optimal properties result in low and variable exposure, leading to compromised efficacy and accentuated toxicity. Enabling technologies are required, therefore, to address issues of low exposure and provide products with predictable and consistent clinical outcomes. Recent advances in science and process engineering have enabled the production of nanometric crystallites that can dissolve rapidly in aqueous media and facilitate increased rate and extent of absorption via a number of administration routes (1). Methods for producing these sub-micron drug crystals or nanoparticles have typically been classified into three categories, including controlled comminution (top down), controlled crystallisation (bottom up), and hybrids of the two approaches (1–3). Size reduction of particles post-crystallisation is often the method of choice in industry, although this presents a number of significant challenges. The mechanical properties of pharmacological actives can often be inadequate for efficient size reduction, with ductile materials in particular showing a tendency to deform rather than fragment, especially at sizes below the brittle-ductile transition (4). Hard abrasive materials at the opposite end of the scale can also be problematic (2), with long processing times often being required to achieve formulations with desirable particle attributes. Recent developments in comminution technology have shown, however, that reproducible sub-micron size distributions of drugs with challenging mechanical properties can be achieved with minimal processing times.

This study presents a new proprietary technology for producing sub-micron crystallites of drugs with challenging mechanical properties (5) that is currently being exploited in the pharmaceutical and healthcare sectors by Lena Nanoceutics Ltd. (Bradford, U.K.). The size reduction system comprises a radially symmetrical sleeve having an axial passage way with an upstream inlet and a downstream outlet. A radially symmetrical rotor sits within the sleeve and rotates at high speed. Grinding media are located within the gap between the rotor and sleeve, which confer high energy impact and shear forces, leading to rapid size reduction of particles in suspension. Methods for producing crystalline nanosuspensions and dispersions in powder form using this technology are described, with evidence of improved dissolution rate for a model ductile compound.

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Methods

Particle size reduction of a ductile model compound (brittle-ductile transition 850 µm, melting temperature 78˚C) was performed using the DM100 size reduction system (Dena Technology Ltd., U.K.). The drug was recycled through the comminution chamber at a solids load of 15% (wt/wt) for 60 min in an aqueous suspension (500 mL) comprising water-soluble polymers and an anionic surfactant. At-line measurements of particle size were undertaken using photon correlation spectroscopy (PCS, Zetasizer Nano, Malvern Instruments Ltd., U.K.), with subsequent evaluation of suspensions by transmission electron microscopy (TEM) under a range of magnification settings.

Processed suspensions were spray-dried in the presence of a water-soluble carrier using the Buchi B-191 mini spray drier with characterization of in-process materials and spray-dried powder by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), TEM, and scanning electron microscopy (SEM).

DSC analysis was conducted using the DSC module of the TA instruments Q2000 series thermal analysis system (TA Instruments Ltd., Crawley, U.K.). Samples of approximately 5 mg were analysed in triplicate using a heating rate of 10 degrees Celsius/min between 25 and 125˚C. XRPD data were obtained using the Bruker D8 powder diffractometer (Bruker, Karlsruhe, Germany). Samples were scanned using a copper Kα radiation source over the 2θ range of 5 to 50˚, with a step size of 0.01˚/min and scan time of 1 sec/step. SEM was carried out using a Quanta 400 SEM (FEI Company, Cambridge, U.K.) at 10–20 kV and working distance of 4 to 10.3 mm. TEM was carried out using the FEI Tecnai 12 system, which was operated at 120kV. Samples were loaded onto 200 mesh copper grids with a Formvar/carbon support film and were then evaluated at a range of magnifications.

Dissolution behaviour of nano-sized formulations was compared to that of a commercial drug substance at pH 7.2 using USPII apparatus (paddle method) with a paddle speed of 50 rpm. Phosphate buffer (pH 7.2) was used as the dissolution media at a volume of 900 mL, with the temperature of the dissolution bath set to 37˚C. Aliquots (5 mL) of the dissolution media were collected at 0, 2, 6, 10, 15, 30, 45, and 60 min and replaced with equivalent volumes of fresh media. Aliquots were then centrifuged at 14,800 rpm for 30 min. The supernatant was collected and analysed for the levels of drug using a suitable HPLC method.

Results and Discussion

Figure 1 is a scanning electron micrograph of the starting material, showing elongated particles with the smallest dimension in the range of 20 to 30 µm and longest dimension in the range of 80 to 120 µm. PCS and TEM showed that trapezoidal particles with an average diameter of approximately 250 nm were produced after 60 min of processing (Figures 2 and 3), with no evidence of particles exceeding 1,000 nm. A small number of particles were observed at sizes less than 50 µm, suggesting that this size reduction method has the potential to achieve further comminution at prolonged processing times. It is clear from these results that particles with diameters markedly lower than the brittle-ductile transition of the model compound can be achieved using this technique.

DSC and XRPD showed that the model compound had maintained its crystallinity and physical form following size reduction and spray drying, respectively. The DSC thermogram for particles isolated from suspension by centrifugation (Figure 4) shows a sharp endothermic melting transition at melting temperature similar to the parent drug substance. After spray drying, XRPD patterns (Figure 5) showed peaks at 2θ positions similar to those of the starting material, suggesting that the nanocrystalline drug had been encapsulated in particles alongside the inert carrier. All other peaks shown in Figure 5 are related to the crystalline structure of the water-soluble carrier.

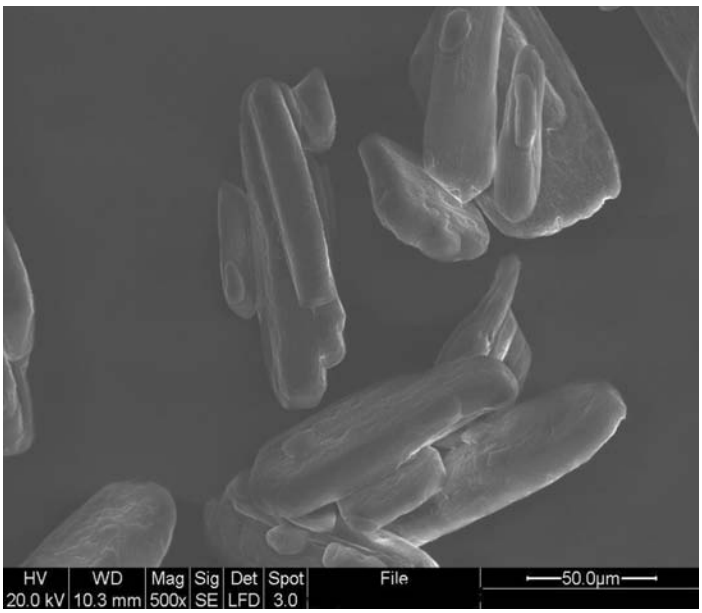

Figure 1. *SEM image of the starting material prior to size reduction.*

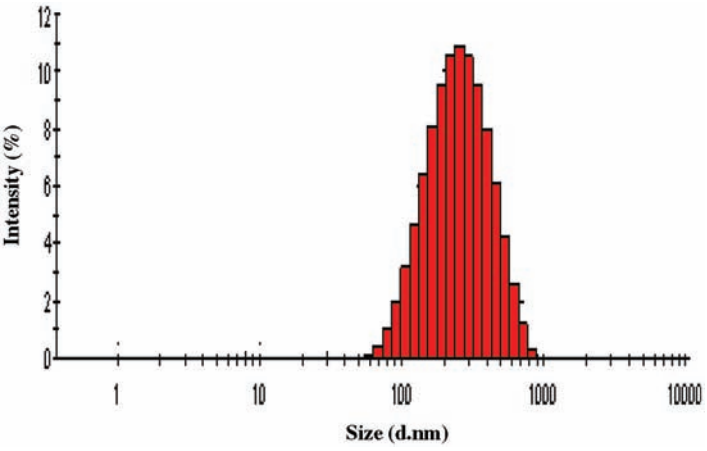

Figure 2. *Particle size distribution by PCS for material processed for 60 min.*

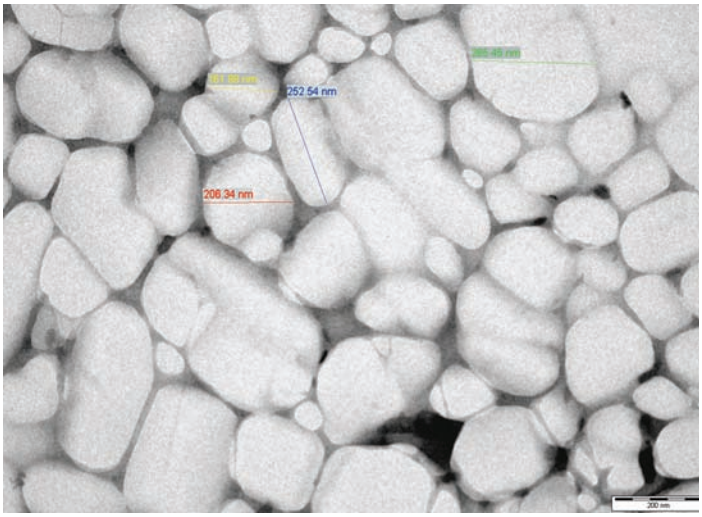

Figure 3. *TEM image showing the particle size of the model material after processing for 60 min.*

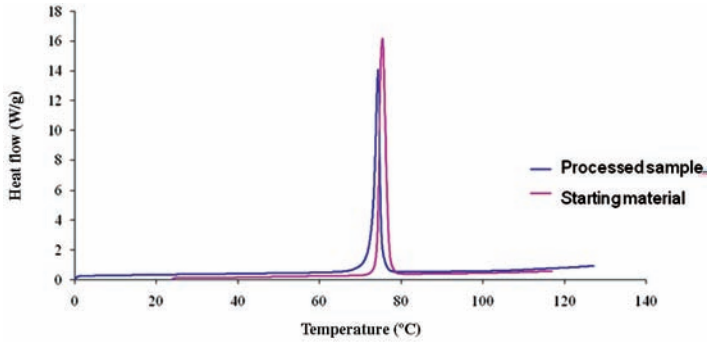

Figure 4. *Representative DSC thermograms showing the melting endotherms for the starting material and crystalline nanosuspension.*

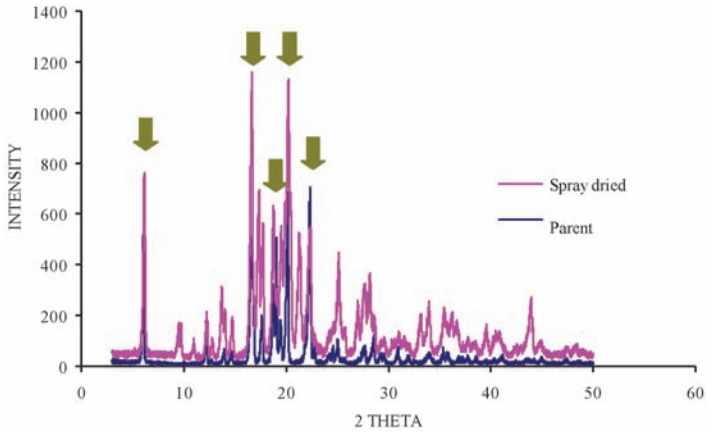

Figure 5. *X-ray powder diffraction patterns of the parent drug substance and spray-dried nanopowder (additional peaks are derived from the inert carrier).*

Spotlight continued on page 20

Spotlight continued from page 19

SEM evaluation of the spray-dried powder showed particles with sizes in the range of 25 to 50 µm (Figure 6) and irregular morphology. The dissolution rate of the spray-dried powder was similar to that of the nanosuspension, with release being almost complete after 2 min (Figure 7). This suggests that no marked particle growth or agglomeration had occurred during spray drying. The dissolution of both liquid and solid nano-formulations was markedly more rapid than that of the starting material, which is explained by the substantial increase in particle surface area for these processed preparations.

Conclusions

These studies have shown that sub-micron sized crystalline particles of a ductile drug can be produced using a novel comminution technique. Particles with sizes smaller than 1,000 nm and average diameter of approximately 250 nm were produced within a period of 60 min with no marked impact on the physical form of the drug substance. Spray drying enabled the nanoparticles to be isolated as a fast-dissolving solid form, which maintained a high level of crystallinity after processing and dissolved more rapidly than commercially available forms of the active pharmaceutical ingredient. Consequently, this new size reduction technique has demonstrated potential to be adopted as means of producing nanoparticles of materials with challenging mechanical properties. Further work is currently being undertaken to evaluate the effectiveness of this size reduction system for processing a range of model compounds.

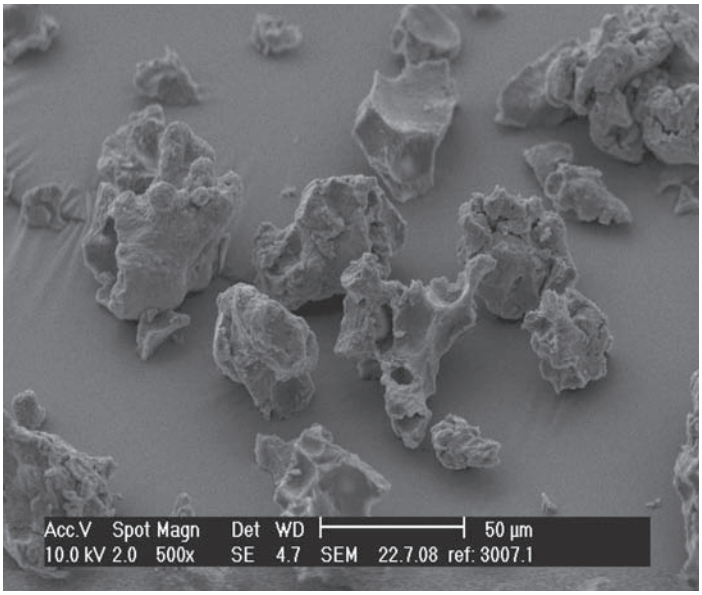

Figure 6. *SEM image of spray-dried powder.*

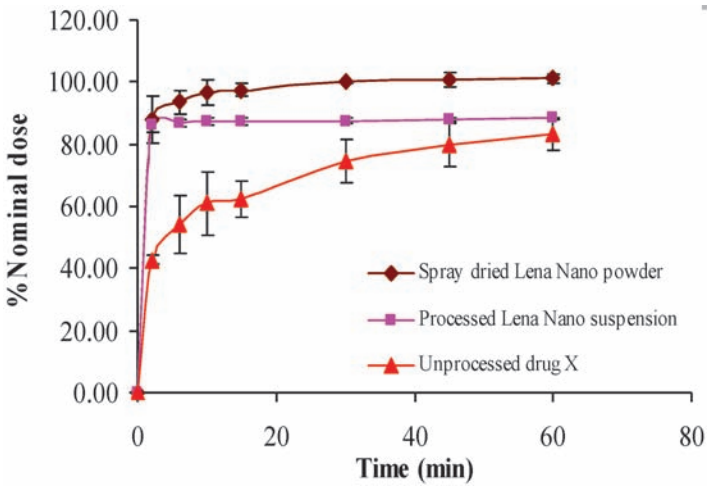

Figure 7. *Comparative dissolution curves for spray-dried nanopowder, nanosuspension, and unprocessed drug substance.*

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Novel Drug Delivery Systems Developed for Animal Health Applications

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Introduction

Comparative medicine has seen a resurgence in the past decade, largely because of the growth of evidence-based veterinary medicine and the increase in knowledge learned from comparative genomics. Diseases such as diabetes, hypertension, skin atrophy, and cancer in some companion animals are similar to those in humans, which allows for parallel development of some therapeutic approaches. The synergy inherent to one-medicine could result in significant cost-savings in product development for both animals and humans.

There are a number of factors that must be taken into consideration when assessing what might emerge as new animal drug products in the future. These factors revolve around economic, societal, and technological issues. However, economic and societal factors are the drivers in business decisions, as without a market new products will not be developed. Projection of transforming technologies such as analytical chemistry, computational sciences, molecular biology, genomics, and material engineering are key realistic approaches to predicting future developments. Economic, societal, and technological issues have led to pharmacology research for treatment of conditions such as aggressive behavior, separation anxiety, and obsessive-compulsive disorder, as well as the launch four years ago of dirlotapide, a drug targeted to reduce obesity in dogs. The result of these societal trends must be that in the future the companion animal market will more sophisticated.

Design of Novel Drug Delivery Systems Intended for Veterinary Delivery

Cattle. In this context, we have developed novel approaches to veterinary formulations of drug delivery systems for different animal species. First of all, we developed a new oral anthelmintic delivery device in order to avoid the economic losses attributed to repeated handling of animals during a treatment. Although these costs are difficult to quantify, they can be considerable. The reduction of the number of handlings allows cattle breeders to realize some economic benefits, which are also seen in a weighting increase at the end of the pasture season and globally in lower infestation rates. Moreover, the level and duration of exposure to gastrointestinal nematode infections are of crucial importance for the development of acquired immunity in first-season grazing calves. An excessive reduction in host-parasite contact by chemoprophylaxis, pasture management, or both causes a diminished level of acquired immunity. The level of acquired resistance is negatively related to the degree of suppression of host-parasite contact. Whether reduced resistance against establishment and development of gastrointestinal nematode infections has a negative effect on weight gain in the second grazing season, depends both on the intensity of the prophylaxis used and on the level of the challenge infection. From cross-sectional serological surveys, it has been shown that parasitic nematode control in first-season grazing calves tends to be overprotective. In addition, possible consequences of overtreatment, besides higher treatment costs and a reduced level of acquired immunity, are more drug residues in animal products and the environment and increased selection for anthelmintic resistance.

Concerning the infestation rate in the pasture (Figure 1), if ruminants are not treated with an anthelmintic drug, the infestation rate first decreases rapidly as the temperature increases in the spring, generally with a minimum of infestation at turnout (yellow arrow). The infestation rate then increases quickly from June on, reaching a maximum in August (red arrow). The disease, also called verminosis, appears most prevalently during July and August when the infestation rate is the highest.

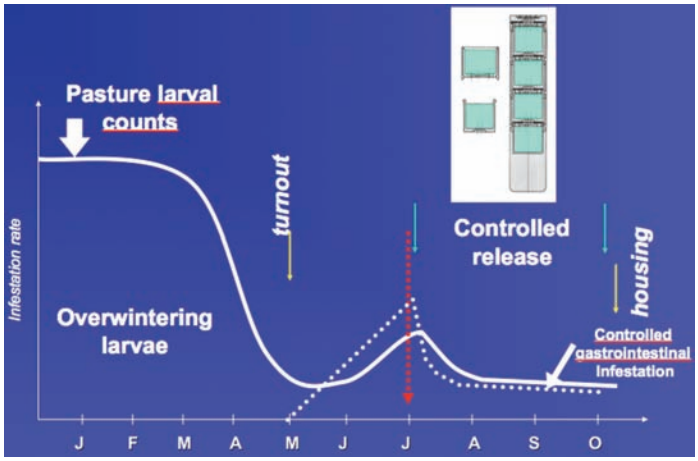

Figure 1. *Controlled gastrointestinal infestation of cattle following the administration of a pulsed and delayed rumino-reticulum device.*

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From these considerations, we developed a new rumino-reticulum device intended for cattle that has a delayed and pulsed release (between the two green arrows on Figure 1) and allows 1) a delayed release (variable following the chemical nature and thickness of the monofilament that is used) (Figure 2); 2) a sequential and pulsed release of the drug; 3) the possibility to increase the amount of dosing released during the grazing season; 4) the possibility to change the anthelmintic agent during the grazing season and thereby avoid the phenomenon of resistance; and 5) the release of the drugs throughout the entire grazing season (1–7).

As mentioned, our new rumino-reticulum devices were constructed by assembling different elements (Figures 1 and 2) containing the drug (indicated in green) and separating one from the other by a degradable monofilament. The first element is covered by a cap pierced by some holes in order to maintain the device (having a density higher than 2.5) in the bottom of the reticulo-rumen of the cattle.

The release of the drug is realized in the following fashion (Figure 2). First, the ruminal liquid dissolves the anthelmintic agent; second, this liquid goes inside the cavity pierced on one side by a hole and separated from one another by a degradable monofilament. At each extremity of the monofilament, a seal prevents the ruminal liquid from entering another compartment before biodegradation. When this monofilament is degraded, the two parts of the compartments separate from one another and allow the ruminal liquid to reach the next compartment. The crossing of the ruminal liquid from one compartment to another one is obviously governed by the chemical nature of the monofilament.

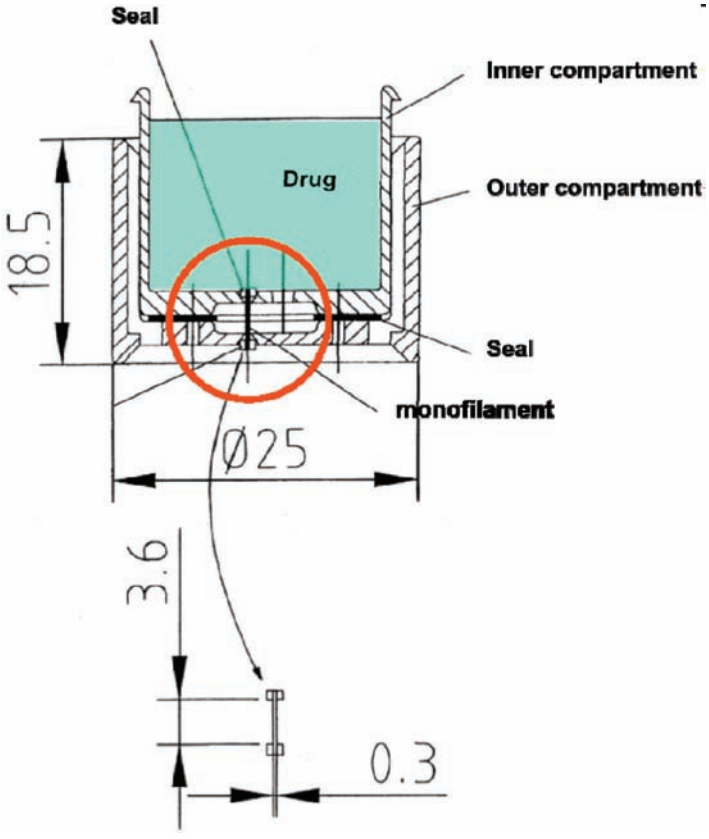

Figure 2. *Rumino-reticulum device showing monofilament.*

Different possible types of biodegradable monofilaments are examined, e.g., a monofilament of Monocryl® and a monofilament of polydioxanone will have, respectively, a breaking time of 22 and 86 days. By choosing adequate monofilaments to design the new rumino-reticulum devices, i.e., by choosing for the first compartment a polydioxanone monofilament, the ruminal liquid is able to progress to the second compartment only after 86 days. Conversely, by choosing another product like a Vicryl® (2/0) monofilament for the next compartments, the breaking time will be only 23 days, fulfilling the requirements for the design of an ideal rumino-reticulum device.

A second application of formulations in the same context was the development of veterinary formulations for treating mastitis. The spread of bacterial infection in connection with cow teats during the milking process results in the spread of the infectious mammary disease known as mastitis (Figure 3). The spread of this disease is generally reduced by the use of antimicrobial compositions. For example, antimicrobial teat dips containing iodine have been shown to be effective against mammary infections and mastitis-causing bacteria. Therefore, ideal formulations should contain an antimicrobial agent and a skin conditioner. Our approaches consisted of a change from emollients in conventional formulations to phospholipids. Phospholipids are suitable since they act as skin conditioners and prevent chapping, peeling, and irritation of the skin. In addition, suitable phospholipids will aid in the flexibility of the skin. In addition to phospholipids and antimicrobial agents, we also added pH adjusters and buffering agents, stabilizers, and thickening agents.

The formulation we used for the different trials was as follows: iodine: 0.5%; poly(ethylene glycol) dimethicone sunflower amidopropyl phosphatidyl glycerol dimonium chloride phosphate complex: 1%; buffering agent (pH = 6): 1%; hydroxypropyl methyl cellulose: 2%; and water: 95.5%. In order to evaluate the novel formulation versus a marketed composition, we studied parameters in a 30-day study of cows who have given birth once (primarous) and those who have given birth more than once (multiparous) for a commercially available teat dip that contains 0.5% iodine with 74% emollients (A) and our composition, which contained 0.5% iodine and 1% phospholipids with 0% added emollients (B). The first parameter

Figure 3. *Mastitis caused by bacterial infection.*

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that was tested was the effect of teat dip on milk yield and composition. To study the impact of the formulation on this aspect, we measured the production of milk (kg/day), fat (%), level of protein (%), percentage of lactose, fat (kg/day), protein (kg/day), and amount of lactose (kg/day). From the results obtained (Table 1), we were able to conclude that there was a statistical significance between the two products only for the percentage of fat.

Pigs. Another application based on improvements in technology for a veterinary formulation was developed for pigs. In the past, an injectable formulation containing florfenicol was developed as a suspension. Obviously, for this kind of formulation the sizes and shapes of the crystals were the critical point during the industrial formulation process, since these factors can have an impact on *in vivo* pharmacokinetics. In order to avoid this problem, we formulated the same drug using the concept of microemulsifying drug delivery systems. Pharmacokinetic studies allowed us to conclude that it was possible to obtain a similar pharmacokinetic for our novel colloidal formulation, in order to obtain a formulation that is easier to produce industrially, more stable, and easier to be injected, and this by only changing the formulation parameters (Table 2, Figure 4).

Dogs. For dogs, we developed a solid oral dosage form containing two active ingredients with different physicochemical characteristics, such as solubility. For these two active substances, it was desirable to obtain prolonged release during a period of about 5 hr. For dogs, the association of spiramycine and metronidazole is recommended for the curative treatment of oral infections. To do this, we prepared multilayer tablets containing the two active drugs in the different layers. From a pharmacokinetic point of view, the aim was reached since it was possible to formulate these tablets with a sustained release for the two drugs (Figures 5 and 6). A similar attempt was realized for the formulation of tablets containing pregabalin, a non-steroidal anti-inflammatory drug, and carbofen, an alpha-2-delta ligand. The goals were also reached since, with the same technology, it was possible to formulate tablets with a sustained release during several hours and allowing the concomitant release of two different drugs having different physicochemical properties and a synergetic activity from a pharmacological point of view (Figure 7).

Conclusions

From our point of view, the general conclusions that can be drawn for the next two decades concern 1) the refinement of our therapeutic collection of drugs intended for the veterinary field; 2) the therapeutic targets will be greatly increased, as has been observed for humans; 3) a higher bioavailability for drugs will be observed due to the design of the most appropriate dosage forms for each animal species; and 4) possibly the most revolutionary conclusion is that this field will be more diverse and specialized in the future by requiring pharmacologists to bridge many sub-disciplines.

Table 1. Effect of teat dip on milk yield and composition with solution A (0.5% iodine + 75% emollients) or B (0.5% iodine + 1.0% phospholipid)

	Primiparous		Multiparous	
Item	**A**	**B**	**A**	**B**
N	26	27	43	42
Milk (kg/day)	40.8	43.3	41.1	41.6
Fat (%)	3.64	3.45	3.40	3.52
Protein (%)	3.09	3.21	3.13	3.13
Lactose (%)	4.96	5.0	4.96	4.95
Fat (kg/day)	1.43	1.39	1.41	1.50
Protein (kg/day)	1.25	1.37	1.29	1.29
Lactose (kg/day)	2.03	2.16	2.04	2.06

Table 2. Composition of a marketed suspension and a new colloidal solution containing florfenicol

Suspension		**Colloidal Solution (Microemulsion)**	
Florfenicol micronized	250 mg	Florfenicol micronized	250 mg
Sodium citrate	50 mg	Soybean oil1	50 µL
Monopotassium dihydrogenophosphate	1.5 mg	Acetylatedmonoglyceride	50 µL
Glucose monohydrate	80 mg	Egg phospholipids	15 mg
Polyvinyl pyrrolidone K25	2 mg	Glycerol	22 mg
Sodium metabisulfite	0.1 mg	HCl or NaOHpH	7.5
Sodium edetate	0.1 mg	Water for injection q.s.	Add 1 mL
Methyl paraben	1 mg		
Propyl paraben	0.5 mg		
Water for injection q.s.	Add 1 mL		

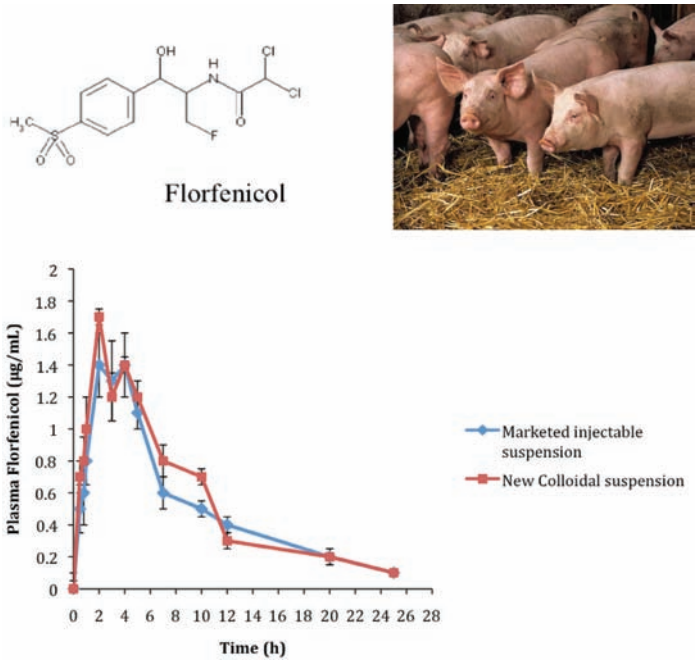

Figure 4. *Pharmacokinetic release of florfenicol following the administration of a marketed injectable suspension and a new colloidal solution, both containing the same concentration of florfenicol.*

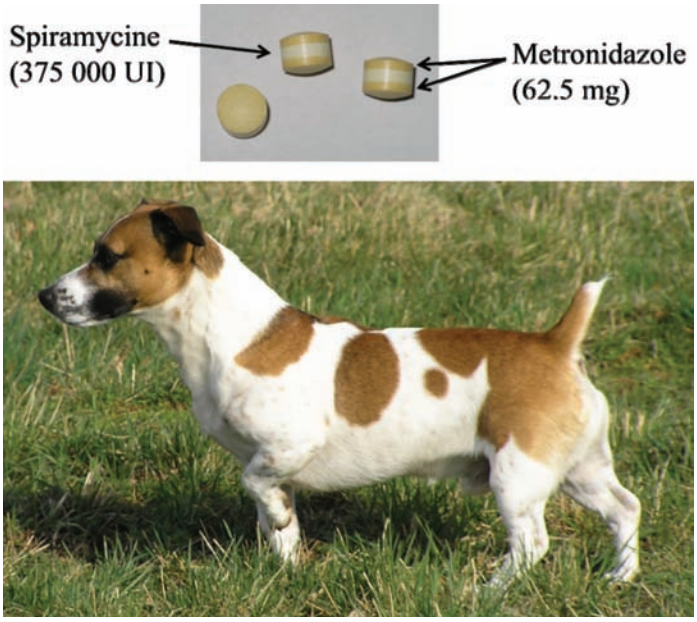

Figure 5. *Design of a multiple-layer tablet for dogs.*

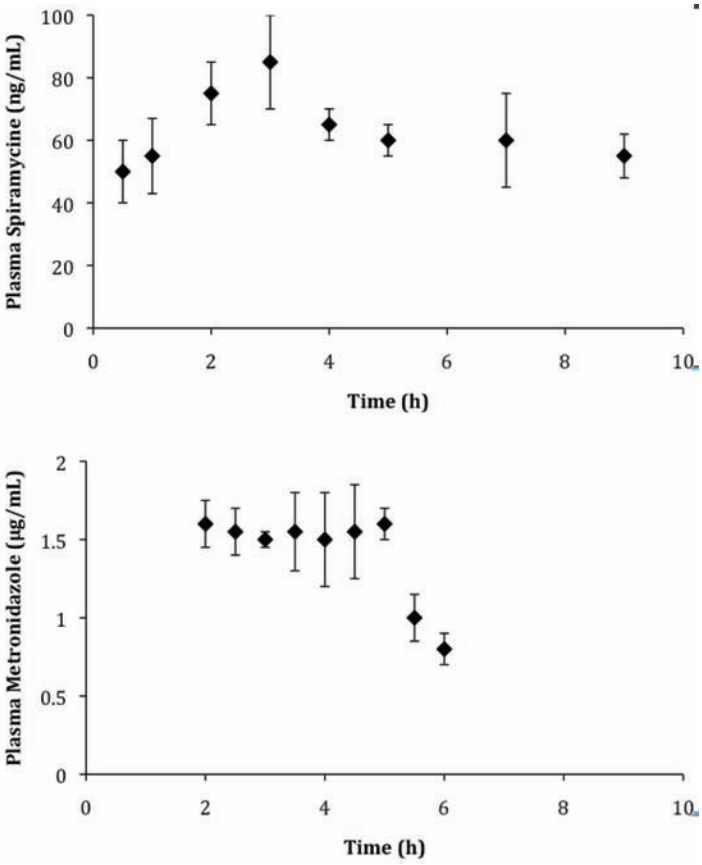

Figure 6. *Pharmacokinetic release of spiramycine and metronidazole in dogs after administration of a multiple-layer tablet containing both drugs.*

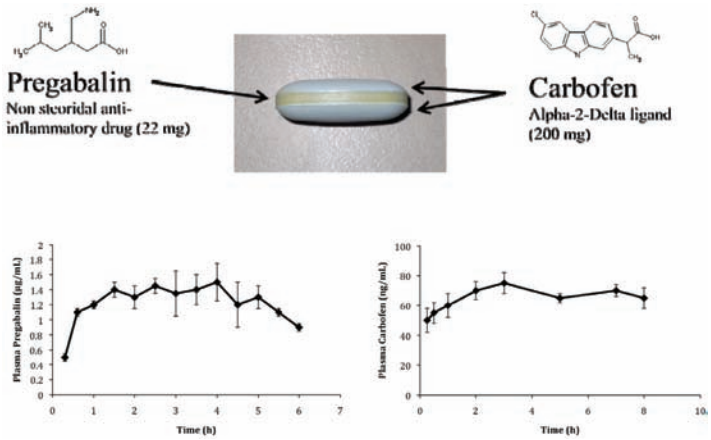

Figure 7. *Pharmacokinetic release of pregabalin and carbofen in dogs after administration of a multiple-layer tablet containing both drugs.*

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Erratum

CRS Newsletter
Volume 27, Number 1, 2010

In the CRS Focus Group article "News from the CRS Nanomedicine Focus Group" by Ghandehari et al. (pages 25–26), the references listed at the end of the article are numbered incorrectly. The first two reference numbers are correct; the remaining references should be numbered 3–7.

Join the 2010/2011 CRS Mentorship Program!

Michael J. Rathbone and Padma V. Devarajan
CRS Young Scientist Mentor:Protégé Subcommittee

The Young Scientists Mentorship Corner is a new column in the *CRS Newsletter* that is dedicated to informing young scientists about the mentorship opportunities that CRS offers. Initiated and run by the Young Scientist Mentor:Protégé Subcommittee, future columns will aim to provide career and networking advice to young scientists. In this first column, Mike Rathbone and Padma Devarajan provide poetic advice to anyone considering joining the CRS Mentorship Program.

The area of controlled release science and technology is increasingly becoming more competitive. A competitive solution for up-and-coming young scientists is to join a mentorship program. Look up the word mentorship in any dictionary and it will tell you that it is "a formal relationship between a student and a professional adult to further the student's knowledge, skills, or career." The CRS Mentorship Program is no different (see poem below). Dedicated to young scientists, the program provides controlled release career opportunities incomparable to any others because of the scientific standing and career experiences of its mentors.

Protégés sign up for the 12-month program at a special "Coffee Morning" that is put on at the CRS Annual Meeting & Exposition. Each protégé is assigned a CRS mentor who is an established member of the Society and who volunteers their time to a protégé for a year. The CRS mentor will provide career advice and help their young scientist to improve their social, career, and networking skills. This they do freely to repay the Society for the many years of value they have derived from being a member of CRS. The mentor may have an industry, academic, or regulatory background…it doesn't matter, what is important is that they all possess a certain quality…a lifetime of experience that they are willing to share. Their goal is to help improve their protégé's performance, make suggestions to solve current critical questions, develop helpful career plans, determine and achieve personal goals, and, possibly, at the end of the day, even help land a better job. All these goals are achieved because a mentor of the quality that the CRS Mentorship Program offers increases the protégé's network of contacts and opens a lot of doors that would normally remain closed.

The CRS Mentorship Program requires the protégé to initiate and maintain the relationship. Indeed, it is understood that any protégé enrolling in the program takes responsibility for maintaining the relationship, be it securing a monthly time to meet or being prepared at meetings with an agenda on what to discuss. Therefore, each protégé should understand before they enroll in the program that the building of a good relationship with their mentor will require a lot of time, work, and effort on their part.

The CRS Mentorship Program offers young scientists excellent opportunities, so think about enrolling for the 2010/2011 Mentorship Program today!!! Expressions of interest in this program can be sent to Michael Rathbone (m.rathbone@griffith.edu.au). ■

The Mentor and the Protégé

The programme "Mentor-protégé"
Planned as a synergy, a Symbiosis tree.
Who is a mentor you may ponder,
And the right protégé!!

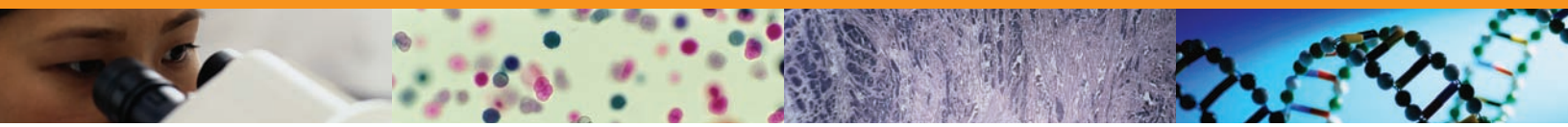
A mentor is not just a teacher
He/She is a guide
Who compels not, to get astride,
But guides you as you ride.

A mentor is a friend in need
To steer you through meandering waves,
To sort the knots and confusions,
Your career path takes

What are the benefits you gain,
When as a protégé, you we rein,
A new seer you ne'er ev'r thought
Would enter your professional domain!!

Networking opportunities galore
Sitting right at home
With this new friend over a period of time,
You'll suddenly realize you've grown!!!!

Padma V. Devarajan



CRS Origins: A Historical Look at the Consumer and Diversified Products (C&DP) Track of CRS

Charles Frey
Coating Place, Inc., Verona, WI, U.S.A.

This article provides a cursory history of the Consumer and Diversified Products (C&DP) track of CRS. Information has been compiled from CRS website information, significant input from Mary Massey (formerly Mary Marshall, a principal founder of the C&DP track), and early members of CRS who helped develop the track, including Harlan Hall, Ron Versic, and Herb Scher.

Elements of controlled release can be found throughout history, but coinage of the term "controlled release" and recognition of it as a field of study can be traced to the early- to mid-1900s. The first commercially successful oral sustained-release products were realized in the 1940s and 1950s. An application involving the controlled release of antifoulants from rubber was conceived in the 1950s. Agrochemical/pesticide applications in the 1970s led to the development of a Controlled Release Pesticide Symposium in 1973 and 1974. This was broadened to Controlled Release of Bioactive Materials in 1977. It was then incorporated as the Controlled Release Society (CRS) in 1978, a non-profit organization with a mission to advance the science and technology of controlled release.

In the early years of CRS, consumer and diversified products was the principal focus of activity. Consumer and diversified products refers here to non-pharmaceutical applications. Agricultural/pesticide and industrial/chemical were the primary interests, but interest rapidly expanded into pharmaceuticals in the 1980s and 1990s following the change in name to include "bioactive materials." The original interest in consumer and diversified products (C&DP) remained through this transition, but it became hidden within pharmaceutical growth.

CRS members with principal interests in C&DP eventually realized that their interests were being only marginally served by the Society. New minds and technologies related to C&DP were not joining or contributing to CRS. This was believed to be due to the lack of visibility of the C&DP elements among the pharmaceutical interests. Those outside CRS could not see the C&DP interest of the CRS; the Society appeared to have developed outsider recognition as a pharmaceutical organization.

Workshops were one vehicle used to foster controlled release education and growth of CRS. A Consumer Products Workshop was led by Jack Burger (Quest International) at a meeting in Amsterdam. Another was chaired by Curt Thies (Washington University) at the 1994 CRS Annual Meeting in Chicago. Mary Marshall, manager of Microencapsulation Research at Southwest Research Institute (SwRI), was invited to the Chicago workshop to present "Submerged Nozzle Encapsulation Technology," which had been practiced at SwRI for more than three decades. (Mary had met Curt Thies and Bob Sparks in 1992 through the Center for Professional Advancement Course on Microencapsulation as the SwRI lecturer.) It was at this CRS Chicago workshop that Mary was first introduced to CRS leaders and began to understand its membership needs. Lecturers at the 1994 Chicago workshop included Thies, Wayne Beimesch (P&G), Zohar Merchant (Kraft General Foods), Jack O'Neill (Sanofi Bio Ingredients), Jack Burger, Robert Sparks (Washington University), Nicholas Peppas (Purdue University), and Hans Junginger (Leiden-Amsterdam Center for Drug Research). After the workshop, most of these presenters met for lunch and discussed how to bring more consumer products researchers into CRS. This discussion led to the formation of the Consumer and Diversified Products (C&DP) Subcommittee under CRS President Dr. Hans Junginger, with the request for Mary Marshall to lead the effort.

Mary Marshall was co-chair or chair of the CRS C&DP Committee from its establishment in 1995 through 1999. Letters were written to identify researchers in the field who wanted to create a strong, continuing presence within CRS for non-pharmaceutical applications. Once a month, between 6 and 12 people joined a conference call for one hour to discuss organizational ideas, workshop topics, and possible presenters. The conference calls were scheduled at 11 a.m. U.S. Eastern time to accommodate members in time zones ranging from California to Europe. Initially, the members and their employers paid for the international calls, but over time, CRS funded a call-in conference number free of charge to U.S. members.

The C&DP Committee quickly decided not to not focus on a workshop offering, but instead to convince CRS to support a C&DP conference. The rationale was that workshops tend to attract researchers new to the field, whereas conferences engage new members as well as support the technical interactions necessary for seasoned researchers. The C&DP Committee requested a stand-alone conference to foster its interests. This was denied by the CRS Board due to concerns about fragmenting the Society and increased financial risks.

Consumer and Diversified Products continued on page 28

Consumer and Diversified Products continued from page 27

A compromise was reached to hold the C&DP conference within the CRS Annual Meeting and to give C&DP stand-alone pages in the annual meeting program book, additional advertising budget, and a dedicated room at the annual meeting for the C&DP sessions.

At the 1998 CRS Annual Meeting in Las Vegas, after three years of preparation, the first of several C&DP conferences was held. The second was held in Boston with the 26th CRS Annual Meeting. By the third C&DP conference (Paris 2000), one-quarter of the CRS Annual Meeting attendance were registered for the C&DP conference. These numbers indicated a successful meeting strategy and a significant continuing interest in C&DP (non-pharmaceutical) areas.

Since the Paris meeting, the C&DP Committee has continued to steer the efforts within the C&DP track of CRS. Its mission is to advance science, technology, and education in the field of controlled release or delivery of non-pharmaceutical active ingredients. The C&DP conference is no longer held as an isolated offering at the CRS Annual Meeting, but it is more seamlessly embedded in the technical program. The C&DP Committee continues to hold teleconferences at 10:00 a.m. U.S. Central time on the second Thursday of each month. This time is focused significantly on preparations for CRS Annual Meetings, including five to six C&DP-focused technical sessions, a C&DP Pearls of Wisdom debate, and a C&DP workshop (if offered). The group continuously looks to new venues to further its mission.

C&DP technical sessions commonly focus on product areas such as foods, nutritionals or nutraceuticals, cosmetics or cosmeceuticals, personal care, agriculture, industrial, flavors, and fragrances, as well as generic elements of controlled release, such as innovative materials, evaluation, stabilization, scale-up, process technology, and matrix interactions. In recent years, the C&DP track has been looking for ways to better represent areas that may not be adequately represented in CRS, such as textiles, environmental concerns, and other more isolated niches.

The C&DP group continues to organize well-attended workshops at the CRS Annual Meeting to help meet its educational goals. These workshops have typically focused on controlled release technologies and have been offered both at an advanced level with field experts presenting the technologies and as more basic instruction for young scientists. A C&DP-organized workshop on evaluation of controlled release products will be offered at the 2010 CRS Annual Meeting in Portland, OR.

By most accounts, the C&DP track is an important element of CRS. Fostering cross-fertilization of ideas between the pharmaceutical and many C&DP areas remains a goal of the track. With its continuing presence as a track within CRS, C&DP looks to maintain its visibility to attract global interest from outside the Society for the benefit of all. Recent new interests in the C&DP track were unaware that their interests were represented within CRS until, by chance, they attended the 2009 CRS Annual Meeting in Copenhagen. They were very pleased to find a CRS track focused in their area. The C&DP group recognizes this as evidence that more effort is needed to bring about the recognition needed to reach its full potential.

In addition to those individuals already mentioned above, early support of the C&DP track came from Harlan Hall (Coating Place, Inc.), Ron Versic (RT Dodge Co.), Terry Mazer (Abbott Laboratories), Judy Roseman (CRS executive director and constant source of assistance, coordination, and encouragement), Alfred Gaertner (Genencor International), Zohar Merchant (Kraft Foods), Adi Shefer (Salvona), Saskia Galema (Unilever), Gulden Yilmaz (ATO-DLO), Eric Abrutyn (The Andrew Jergens Company), Denis Poncelet (ENITIAA and Bioencapsulation Research Group), Gary Cleary (Corium, CRS president), Robert Gurny (University of Geneva, CRS scientific secretary), Susan Cady (Merial, CRS president and treasurer), James Paik (JSP development, Kellogg), Chul Soo Shin (Yonsei University), Niraj Vasishtha (SwRI), Todd Becker (Genencor International), Kinam Park (Purdue University, CRS president), Michael Rathbone (Griffith University, CRS Board of Scientific Advisors), Anil Gaonkar (Kraft Foods), Irv Jacobs (Particle and Coating Technologies), Richard Wilkins, Jamileh Lakkis, Quin Qui Zhao, Margaret Courtney, and others. Since the 2004 CRS Annual Meeting in Hawaii, a "newer generation" of the C&DP steering committee has become active. The group has also been joined by others who realized the same passion. In addition to persons already mentioned, contributors to the C&DP effort in recent years have included Cathy Ludwig, Doug Dale, Claudio Ortiz, Teresa Virgallito, Ruth Schmid, Nava Dyan, Paul Richardson, Birgit Schleifenbaum, Chris Soper, James Oxley, Chris Barbé, Fanwen Zeng, Raja Sivalenka, Kelly Miller, Nicole Papen-Botterhuis, Zhibing Zhang, and Igor Bodnar.

A challenge for the C&DP track has been and remains the reluctance of many C&DP technology areas to share work and findings. Many of these technologies rely commercially on patent protection or trade secrets for their success. Sharing exposes their technology to competition; the commercial element trumps any potential advancement that might be realized from sharing. In the health/pharmaceutical fields, this hierarchy may possibly be reversed somewhat due to a more core societal benefit and recognition. The C&DP track would benefit greatly if its application base could find a way to reverse the practice of its industries. Sharing work at CRS Annual Meetings through submission of podium and poster abstracts is one way to do this. Publication of C&DP scientific papers in the *Journal of Controlled Release* is another. A separate journal for controlled release in C&DP areas has been suggested in recent years; however, it may not be realized without momentum built within the Journal of Controlled Release.

The C&DP track continues to look forward to growing recognition of, and contributions to, its mission. This mission is consistent with the mission of CRS and should help optimize the value of membership in CRS. ■

Consumer and Diversified Products (C&DP) Prepares for Portland

For the past 15 months or so the CRS Consumer and Diversified Products (C&DP) Track steering committee has been making plans for the 2010 CRS Annual Meeting in Portland, OR. C&DP Technical Program Chair Dr. James Oxley (Southwest Research Institute, U.S.A.) and Co-chair Dr. Christophe Barbé (Ceramisphere Pty. Ltd., Australia) have organized a five-session program with elements of the "green" theme of the Portland meeting. These sessions focus on several of the areas under the Consumer and Diversified Products umbrella, including personal care, food, environmental, nutritional, and industrial products. Details of the sessions are summarized below.

Novel Materials and Release Systems
Monday Morning • July 12

Invited Speaker: *Improving the Performance of Lipid-based Formulations Using Specifically Engineered Nanoparticle Layers* – Clive Prestidge

Safer Than Safe: Sol-Gel Encapsulation of Sunscreens – Howard Epstein

Antimicrobial Activity of Zeolite-exchanged and Liposome-encapsulated Silver Ions – Claire Martin

Regional Drug Absorption Study in Canines with Intelligent Pill System – Hans Zou

A New Encapsulation Process Tool: The Encapsulation Printer – Nicole Papen-Botterhuis

Nanoparticles and Fibers for Controlled Release
Monday Afternoon • July 12

Invited Speaker: *Gold Nanocages for Controlled Release with Near-Infrared Light* – Younan Xia

Nanoparticles by Spray Drying: The New Technology of the Büchi Nano Spray Dryer B-90 Encapsulation with Electrospinning for Food Applications – Igor Bodnar

Preparation of Atactic Poly(vinyl alcohol)/Gelatin Blend Nanowebs by Electrospinning – Won Seok Lyoo

Drug and Protein-eluting Core/Shell Fibers for Various Biomedical Applications – Meital Zilberman

Encapsulation for Environmental Protection
Tuesday Morning • July 13

Invited Speaker: *TBA* – Nissim Garti, The Hebrew University of Jerusalem

Invited Speaker: *Introduction to Self-healing Materials Technology and Applications in Corrosion-Resistant Self-healing Coatings* – Gerald Wilson

Comparing the Influence of the Film-coating Formulation on the Oxygen Gas and Water Vapour Transmission Rates – Eva Wagner

Water Barrier Coatings from Biopolymers with Specific Release Properties – Ted Slaghek

Encapsulation of Cells and Microorganisms
Tuesday Afternoon • July 13

Invited Speaker: *Encapsulation for Controlled Delivery of Probiotic Cultures in Foods* – Claude Champagne

Hypoxia Detection in Living PEG-encapsulated Pancreatic Tissue: A Novel Fluorescent Marker System – Matthew Skiles

Characterization of Stabilized Formulations of the Atrazine-degrading Bacterium Pseudomonas *sp. Strain APD* – Scott Stelting

Synthetic Blood Cells: A Biomimetic Approach for Theranostics – Nishit Doshi

Electrospinning Droplet-assisted Synthesis of Magnetic-responsive Insulin-loaded Alginate Microcapsules – Keng-Shiang Huang

Environmentally Friendly and Biodegradable
Wednesday Morning • July 14

Invited Speaker: *Microencapsulated Toxins—A Trojan Horse Approach to the Control of Zebra Mussels* – Geoffrey Moggridge

Effect of Pepsin on the Release of Alpha-tocopherol from Wheat Protein Microspheres – Harmit Singh

Nanoporous Silicon Particles with Tailored Features for Controlled Biodegradation – Jonathan Martinez

C&DP Prepares for Portland continued on page 30

C&DP Prepares for Portland continued from page 29

Biologically Responsive, Amino Acid-based Polyesteramides and Polyesterurethanes for Drug Delivery – Aylvin Dias
Highly Efficient Encapsulation Processes for a Wide Range of Industrial Applications from Food to Pharmaceutics to Consumer Products – Thorsten Brandau

In addition to these technical sessions, a C&DP workshop has been organized by Chairs Dr. Nicole Papen-Botterhuis (TNO Science and Industry, the Netherlands) and Dr. Zhibing Zhang (University of Birmingham, U.K.). Workshop details are summarized below.

Characterization of Nanoparticles and Microparticles Using State-of-the-Art Techniques
Saturday • July 10

Introduction to Characterization of Nanoparticles and Microparticles Using State-of-the-Art Techniques – Nicole Papen-Botterhuis
Electron Microscopy Techniques for Micro- and Nano-particle Analysis – Wim Busing
Light-scattering Techniques for the Measurement of Size and Zeta Potential of Nanoparticles – Ulf Nobbmann
Aspects of Characterization and Toxicology of Nanoparticles – Nancy Monteiro-Riviere
Overview of Existing Characterization Techniques Used in the Pharma Industry – Samir Haddouchi
Characterization of Polymeric Materials Using DSC, X-Ray Diffraction (XRD) and Nuclear Magnetic Resonance (NMR) – Finizia Auriemma
Methods Based on Confocal Laser Scanning Microscopy in the Characterization of Microcapsules – Dominic Rochefort
Fundamentals of Permeation and Applications in Materials Design of Controlled Release Systems – James Paik
Studies on Coated and Encapsulated Components with Dynamic Gastrointestinal Models – Rob Havenaar
Determination of the Mechanical Strength of Microcapsules by Micromanipulation and the AFM – Zhibing Zhang

The C&DP track strives to represent its core interests in non-pharmaceutical controlled release technology and is looking forward to a stimulating and engaging exchange generated from the technical sessions and workshop. Thank you to all involved!

For more information on the 2010 CRS Annual Meeting & Exposition, please visit the CRS website at www.controlledreleasesociety.org/meeting. ■

CRS Italian Chapter

Paolo Caliceti
Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Padua, Padua, Italy

The annual CRS Italian Chapter workshop was held in Modena, Italy, November 5–7, 2009. The subject of the workshop, "Multidisciplinary Strategies to Target the Central Nervous System," attracted more than 130 delegates from both academia and industry, including a few international scientists. Thanks to CRS and our other sponsors it was possible to support the participation of CRS members, young scientists in particular. Furthermore, the workshop was broadcast with more than 300 contacts. Full registration is know available at the website (www.tv.unimore.it/media/medicina/vandelli/index.html).

At the opening, the co-chair of the workshop, Prof. Vandelli (Univ. of Modena), and the CRS Italian Chapter president welcomed the delegates and presented upcoming chapter and general CRS activities. The attendees were warmly invited to advise and join the mini-symposium on oral delivery (Toward Drug Delivery Systems: When the Drug Doesn't Like the Standards) held in Milan, December 2, 2009; the CRS-AFI meeting (Innovation in Pharmaceutical Products and Processes) held in Rimini, June 10, 2009; and, in particular, the CRS Annual Meeting & Exposition to be held in Portland, OR, July 10–14, 2010.

The CRS Italian Chapter president introduced the workshop, underlining the aims of the association: education of young and senior scientists through the dissemination of drug delivery knowledge according to multidisciplinary perspectives; promotion of industrial and academic collaborations; and creation of effective scientific national and international networks. The attendees were encouraged to interact as main actors in the workshop, which was organized in a familiar atmosphere to make everybody, young scientists in particular, feel comfortable and free to ask any question and contribute to the discussion.

The workshop program continued with the scientific sections, excellently directed by the chairs who stimulated audience contributions. Outstanding Italian and international scientists were invited to highlight the interdisciplinary character of brain delivery. Biological mechanisms and clinical aspects of neurodegenerative diseases and CNS-related malignancies of haematologic and Huntington's disease were presented by Prof. Agnati and Dr. Riva (University of Modena) and Prof. Cattaneo (University of Milan). Prof. Delie (University of Geneve) described the use of an *in vitro* blood brain barrier model as a reliable tool for brain delivery studies. The development and exploitation of HIV-1 viral protein Tat and vectors for receptor-mediated transcytosis in brain delivery were reported by Prof. Pittaluga (University of Genua) and Prof. Khrestachatisky (University of Marseille), while Prof. Masserini (University of Bicocca, Milan) and Prof. Constantino showed the use of nanoparticles in brain targeting and Alzheimer's disease. On the industrial side, Dr. De Santis (Sigma-Tau) disclosed results obtained in collaboration with the European Institute of Oncology on avidin-biotin systems for brain targeting. Dr. Benichou (Genzyme) and Dr. Gaviraghi (Siena Biotech) described the industrial strategies and platforms for SCN disease targeting and identification of brain-penetrating new drugs.

Multidisciplinary Strategies to Target the Central Nervous System workshop. Proff. Giuseppe De Rosa, Roberta Cavalli, and Bernard Benichou.

The main lectures introduced a variety of scientific reports from senior and young scientists on the use of drug delivery systems for brain targeting. Dr. Esposito (University of Ferrara), Dr. Brioschi (Italian Auxol Institute of Turin), Dr. Craparo (University of Palermo) and Dr. Vighi (University of Modena) presented results obtained with lipid nanoparticles. The use of polymeric nanoparticles, mainly based on chitosan derivatives, were reported by Dr. Trapani (University of Bari), Prof. Dal Piaz (University of Ferrara), and Dr. Mennini (University of Florence). Liposomes and niosomes for brain delivery were discussed by Dr. De Rosa (University of Naples) and Dr. Bragagni (University of Florence). Bioconjugation strategies to enhance drug delivery in the central nervous system were reported by Dr. Iannitelli (University of Chieti) and Dr. Denora (University of Bari). Dr. Salmaso (University of Padua) presented results obtained with ascorbic acid as a targeting agent, while Prof. Fresta (University of Catanzaro) reported results obtained by his research group on an *in vivo* study for the BBB passage evaluation of a colloidal drug delivery system. Finally, Dr. Poggi (Bracco Imaging) and Prof. Smith (University of Aarhus) presented brain imaging by magnetic resonance and positron emission tomography.

Prof. Vandelli, Prof. Fresta, and Dr. Bragagni were charged with the concluding remarks. On behalf of the CRS Italian Chapter, Prof. Fresta thanked Proff. Vandelli and Forni and Drs. Tosi and Ruozi and all the staff of the University of Modena, including students, for the excellent organization and logistical support provided to the delegates. Dr. Bragagni, as a representative of the young scientists, reported his positive comments and thanked everyone for the effort to involve all attendees in the activities.

The workshop was dedicated to the memory of Maria Edvige Sangalli (Didi), treasurer of the CRS Italian Chapter, colleague, and friend. ■

Chapter News continued on page 32

A Meeting of the Minds When Drug Delivery to the Brain Was the Topic at the Joint FDB/NZCRS Conference

Pranav Karmwar and Sarah Gordon
School of Pharmacy, University of Otago, Dunedin, New Zealand

More than 90 delegates from academia and industry participated in the science-intensive and exciting multidisciplinary 12th Formulation and Delivery of Bioactives conference, a joint conference of the Formulation and Delivery of Bioactive (FDB) Research theme of the University of Otago and the New Zealand Chapter of the Controlled Release Society. One of the attractive and enriching aspects of this conference was that it brought people together with an interest in both formulation and delivery. Much science these days happens at the interface between disciplines, and this conference created an excellent opportunity for interactions and collaborations between academic and industry representatives. The first day of the two-day conference was devoted to delivery to the brain. The second day of the conference was devoted to delivery of large molecules, with presentations from international and local speakers who challenged and stimulated us with their knowledge and thoughts.

The conference began with a welcome from Prof. Ian Tucker (FDB theme convenor, University of Otago, New Zealand). The introductory presentation was given by Dr. Mark Habgood (University of Melbourne, Australia) on the barriers to the delivery of drugs to the injured brain. Dr. Habgood also shed light on the mechanisms involved in the restricted diffusion between the blood and the brain and how they might impact the delivery of therapeutics into the central nervous system (CNS). Current research was discussed by Dr. Joseph Nicolazzo (Monash University, Australia) on the impact of the blood brain barrier in facilitating and preventing drug access into the CNS. Further, Prof. Ian Tucker talked about the strategies for delivering neuropharmaceuticals into the CNS and targeting them to specific regions of the brain. The first session of the conference came to an end after the talk by Dr. Ignacio Segarra (International Medical University, Malaysia) on mechanism analysis of tissue distribution kinetics. Different transporters and strategies for crossing the blood brain barrier and improving bioavailability was given considerable attention. Dr. Hu Zhang (University of Otago, New Zealand) presented an overview of microdialysis in brain research, and Dr. Ruth Empson (University of Otago, New Zealand) talked about polymeric devices for the delivery of neuroactive compounds to the cerebellum. In a complementary talk, Dr. Natalie Medlicott (University of Otago, New Zealand) presented insights into formulation strategies to optimise the release of a neuroactive factor, including consideration of the mechanisms that modify the release characteristics of these formulations to the brain.

Dr. Raid Alany (NZCRS president) (left) with CRS keynote speaker Prof. Gerrit Borchard (right). (Photo courtesy of Chompak Pirayavaraporn, University of Otago)

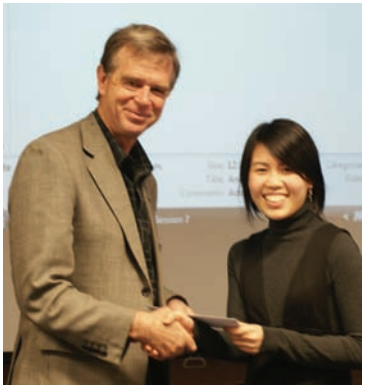
The afternoon session on the first day focussed on two aspects: barriers to brain delivery and transporters and strategies for brain delivery. There was a session of rapid-fire oral presentations of posters followed by oral presentations by postgraduate students from New Zealand and Australia. One of the thrilling and stimulating facets of this conference was that it provided a platform for future scientists to present their work and be acknowledged in the scientific world. Immediately after this was the AGM for the CRS New Zealand Chapter (NZCRS), after which everyone headed to Glenfalloch Restaurant on the Otago Peninsula for the conference dinner.

Day two of the conference signalled a change in theme to challenges in the delivery of large molecules. The scene for this theme was very nicely set by the NZCRS keynote speaker Prof. Gerrit Borchard (University of Geneva, Switzerland). Prof. Borchard gave a comprehensive and informative overview of current trends in the delivery of macromolecules and highlighted the increasing move in both his research as well as the general area of drug delivery "from a mechanical approach to a more biological perspective." He also provided some interesting insights into promising technologies for future delivery applications, such as the use of inkjet printer technology for delivery of functionalised polymers in the area of chronic wound healing and the employment of implantable detector-coupled LED tattoos for display of diagnostic information (such as blood glucose levels) on the skin.

Following the keynote address, Assoc. Prof. Lene Jørgenson (University of Copenhagen, Denmark) gave a very interesting presentation on the issues surrounding delivery of peptide and protein actives, with a specific focus on protein adsorption at interfaces. An excellent overview of both the techniques available to study adsorption effects and formulation initiatives capable of countering these effects was presented.

The second session of the day was opened by Prof. Thomas Rades (University of Otago, New Zealand), who not only effectively outlined the use of nanoparticulate carriers to improve the immunogenicity of peptide and protein antigens, but also sparked a lively discussion on the correct pronunciation of the word "liposome." This session was rounded off by very informative and complementary talks by Dr. Doug Eckery (Victoria University,

New Zealand) and Dr. Arlene McDowell (University of Otago, New Zealand) addressing the significant challenges surrounding delivery of large molecules to wildlife. The afternoon session of day two consisted of submitted oral papers and was largely composed of student presentations. A diverse range of topics was covered in this session, with a strong focus emerging on the use of particulate carriers for drug delivery applications.



Top to Bottom: Prof. Ian Tucker (FDB theme convenor) with 2010 FDB Poster Prize winner Thunjiradasiree Kojarunchitt; NZCRS Student Prize winner Nicky Thomas with Dr. Raid Alany (NZCRS president); and Dr. Raid Alany with NZCRS Student Prize runner-up Admire Dube. (Photo courtesy of Chompak Pirayavaraporn, University of Otago)

With the 12th joint FDB and NZCRS conference drawing to a close, the awarding of prizes and final formalities were initiated. The FDB Poster Prize winner was announced by Prof. Ian Tucker as Thunjiradasiree (Ice) Kojarunchitt (University of Otago, New Zealand). In his closing remarks Prof. Tucker stated his intention to undertake study leave in 2011 and formally handed over his duties as convenor of the FDB theme to Prof. Thomas Rades for this time. The NZCRS Student Prizes were then announced by NZCRS President Dr. Raid Alany. As is the case every year, the student presentations were of an exceptionally high standard, and it was noted that a winner was hard to call. The first prize in this year's competition was awarded to Nicky Thomas (University of Otago, New Zealand), with Admire Dube (Monash University, Australia) being announced as the runner up.

As usual this year's meeting brought together a great mix of international and local speakers from a wide variety of research areas within the formulation and delivery theme. The traditionally collaborative atmosphere of the conference was as strong as ever this year, cementing the success of this 12th meeting and creating anticipation for lucky number 13 next year. ■

Novel Methods for Developing Clinically Relevant Product Specifications[1]

Marilyn N. Martinez,[2] Arzu Selen,[3] and Roger Jelliffe[4]

A workshop co-sponsored by the American Association of Pharmaceutical Scientists and the Controlled Release Society, Novel Methods for Developing Clinically Relevant Product Specifications, will be held Saturday, November 13, 2010, at the Morial Convention Center, New Orleans, LA. The workshop will be held immediately prior to the APPS Annual Meeting (http://www.pswc2010.org/)

With a focus on dosage forms with complex drug release patterns, the Controlled Release Society (CRS), in collaboration with the American Association of Pharmaceutical Scientists (AAPS), is sponsoring a workshop to explore mechanisms for developing clinically relevant product specifications through the integration of process and product understanding with pharmacokinetic/pharmacodynamic (PK/PD) methods. This integration involves the identification of *in vitro/in vivo* correlations/relationships (IVIVC/R) that support the development of drug dissolution/drug release criteria that predict the product's *in vivo* performance in a patient population. While an IVIVC/R is the ideal goal, it may not be easily achievable for some drugs using traditional methods. Therefore, as we explore alternate approaches to IVIVC/R, a related consideration is a context-driven specification setting (i.e., quality target product profile (QTPP)-driven product specification) that relates *in vitro* product specifications to a parameter of clinical value (e.g., an early T_{max} for a sleep aid or a certain release pattern for a cardiovascular drug). In so doing, the selected product profile acceptance criteria will support the intended *in vivo* release pattern, which in turn relates to some therapeutic response.

Pharmaceutical QbD (quality by design) is a systematic, scientific, risk-based, holistic, and proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (1). Inherent in this definition is the need to understand how varying the product *in vitro* release characteristics (which can be highly complex for modified release formulations) will influence the *in vivo* drug release profile, patient drug exposure, and, ultimately, the patient's clinical response.

Implementation of QbD principles to drug development is bringing in novel approaches and considerations that can result in considerable patient health benefits. How best to integrate biopharmaceutics into QbD for the *in vitro* drug release/dissolution specification setting was explored in a 2009 workshop (Quality by Design and Applied Biopharmaceutics), which was co-sponsored by Extension Services in Pharmacy, School of Pharmacy, University of Wisconsin, and the FDA in cooperation with AAPS (www.pharmacy.wisc.edu/esp/prog/fdauwqbdfiles/Bio%20and%20QbD%20conference-two%20week%20update.pdf). The 2009 workshop identified nine areas for advancement that would lead to effective integration of biopharmaceutics into QbD, resulting in the development of *in vitro* drug release/dissolution acceptance criteria that can link product characteristics to the drug product's desired *in vivo* performance (2). Such specifications would be guided by optimized use of biopharmaceutic tools and QbD principles. While these nine areas will be further reviewed and discussed in the 2011 workshop (a continuation of the 2009 workshop), the current CRS-AAPS workshop is dedicated to in-depth discussions on exploring methodologies for integrating product and process understanding and PK/PD approaches that reflect the relationship between a drug product and its performance in the target patient population. In so doing, the objective is to explore the feasibility of using this novel approach to generate clinically relevant product acceptance criteria for these complex dosage forms (2).

Put simply, consistent with the FDA Q8 (R2) guidance document (1), product specifications should ensure that pharmaceutical products function as designed for meeting patient needs and the intended *in vivo* product performance. Strategies for accomplishing this objective can vary from an empirical to a systematic mechanistic approach. The empirical (minimal) approach bases product specifications on batch data at the time of registration, and these specifications serve as the primary means of product control. Alternatively, the systematic (enhanced) QbD approach incorporates product specifications as a component of the overall quality control strategy, where the specifications are based on the desired product performance (www.ich.org/LOB/media/MEDIA4986.pdf).

IVIVCs are used to bridge *in vitro* drug release characteristics to *in vivo* product performance. They are used for setting dissolution specifications and as a surrogate for *in vivo* bioequivalence assessment for oral extended release products. However, there are challenges in developing such relationships for drug products with complex release mechanisms. Therefore, alternative mechanisms for linking *in vitro* release profiles to clinical outcomes may need to be considered.

1 The content of this manuscript reflects the opinions of the authors and does not reflect official policy of the FDA. No official support or endorsement by the FDA is intended or should be inferred.

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One of the challenges in developing *in vitro* and *in vivo* correlations (e.g., for parenteral extended release dosage forms) is that the *in vitro* test conditions result in drug release occurring over a period of hours and may even have an initial burst release compared with the *in vivo* release duration of weeks, months, or even years. While time scaling is possible in certain cases for developing *in vitro* and *in vivo* correlations and can lead to dissolution/release acceptance criteria with clinical relevance, the methodology is fairly complex. Along with the 1997 CDER guidance titled "Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlations" (3), a good general reference on this topic was published by Emami in 2006 (4). While some success at establishing IVIVCs has been achieved with oral dosage forms, it is far more challenging to develop similar correlations for parenteral modified release formulations (5). It is also important to recognize that even in situations where an IVIVC can be defined, it is generally based on *in vivo* data generated in normal healthy volunteers (6). Therefore, such correlations fail to describe the variability in drug pharmacokinetics (including variation in the *in vivo* drug release characteristics) that may influence drug exposure in the actual patient population or how such variability can influence the therapeutic outcome across a targeted patient population.

To establish clinically relevant product specifications (also referred to by some as QTPP-driven product specifications), there is a need to link *in vitro* drug release to clinical outcome. Such linkages necessitate the identification not only of exposure–response relationships in the patient population, but also the relationships between delivery rate and response. This will enable assessment of effect as we vary *in vitro*, and hence *in vivo*, drug release characteristics. In so doing, these models translate *in vivo* outcomes to *in vitro* release goals, thereby enabling the manufacturing scientist, drug delivery scientist (including product formulator and biopharmaceutics experts), pharmacometrician, and clinical scientist to collaborate on the establishment of *in vitro* product release specifications that have clinical relevance.

Ultimately, such information (relationships, models) can be used to integrate the range of product design variables influencing product performance, the kinetics of the drug, the drug uptake characteristics associated with the administered dose, the covariates unique to the targeted patient population, and the clinical outcome in the targeted patient population. This paradigm is consistent with the concept of QTPP, which describes the relationship between product quality characteristics and some reproducible therapeutic benefit as stated in the label.

Based on ICH Q8 (R2) (which has been incorporated in the previously mentioned FDA/CDER guidance document), the QTPP can include such factors as dosage strength(s), intended use in a clinical setting, and drug release or delivery attributes (e.g., dissolution) affecting the pharmacokinetic characteristics of the drug product dosage form being developed. Thus, the QTPP can guide the establishment of formulation strategies and product specifications. With this in mind, it is evident that the development of clinically relevant population models can serve as an important component of establishing the QTPP.

While the latter goal is nice in theory, it raises a host of important logistical concerns. For example, how does one determine "clinical relevance" and translate that to product specifications? Is it even feasible? If yes, under what conditions is it feasible? What modifications would need to be introduced into the product development process to achieve such goals? How would such information be used?

Figure 1 is intended to further illustrate the interrelationships associated with this approach to the establishment of product specification with clinical relevance. We start with the intended clinical target. We consider the desired clinical outcome, dose, and dosing regimen and the intended product release attributes. This is considered the QTPP, which serves as a focal point during product formulation development. In parallel with identification of critical process parameters and the impact of changes in process and formulation to drug release, preliminary population PK/PD models can be developed based on prior experience with the active pharmaceutical ingredient or knowledge gained from a similarly acting drug moiety. As the product progresses to the clinic in Phase II studies, the model should be refined to reflect clinical outcomes in the intended patient population. The model would also allow characterization of the necessary *in vitro* release characteristics. Based on these clinically relevant models, the relationship between altered product release specifications and therapeutic outcomes in the patient population can be explored. *In vitro–in silico–in vivo* correlations can be used to link the *in vitro* release test data to the patient drug exposure characteristics and, ultimately, the therapeutic response. As more data are generated, additional iterations of this paradigm may be appropriate. Ultimately, with a well-characterized modeling approach, process understanding and critical quality attributes and *in vivo* performance of the product can be linked, and when changes occur in critical process parameters and/or in the formulation that result in changes in drug release properties, *in vivo* performance of the product can be predicted.

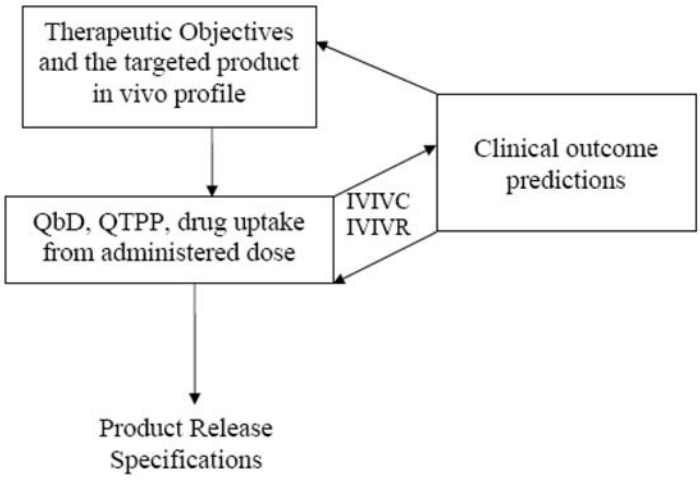

Figure 1. *The paradigm.*

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Satellite Workshop continued from page 35

This model includes not only IVIVC but also IVIVR (*in vivo/in vitro* relationships representing novel approaches). Use of the term IVIVR provides the opportunity to establish a range of relationships that may extend beyond those listed in the 1997 CDER/CBER guidance. For industry, such flexibility may be particularly important as we consider the complex drug delivery platforms and drug release characteristics associated with products being developed for parenteral administration.

If we expand on the QbD concept, the following diagram (reprinted with permission from Dr. Moheb Nasr) identifies two main areas, product/process design and development and risk assessment and risk control (Figure 2).

The information for this portion of the workshop (QbD and design space) will be covered by Drs. Raafat Fahmy (Design Space and Product Specifications: A Risk Assessment Approach) and Moheb Nasr (Quality by Design: Impact on Drug Development and Its Global Applications). Dr. Arzu Selen will follow these talks with examples of how QTPP can guide development of drug products with release characteristics critical for the desired clinical outcomes, ultimately leading to drug dissolution/release acceptance criteria that link CQAs to the desired *in vivo* drug performance.

Following these presentations, we will consider how an investigator can define the targeted *in vivo* product performance and how one can link that targeted performance to a "clinically relevant" specification. Within this workshop, we will explore the feasibility of using PK/PD relationships and/or simulation approaches for exploring potential relationships between *in vivo* drug release, drug exposure, and clinical outcomes in a patient population. Drs. Kevin Johnson and John Crison will share examples of application of computational tools to describe and guide drug dissolution/release patterns and how patient gastrointestinal characteristics need to be considered for development of oral drug delivery platforms. Dr. Adrian Dunne will follow with a discussion of how nonlinear mixed-effect models can be used to link *in vitro* and *in vivo* drug release for complex dosage forms.

These talks set the stage for the next step, which is linking these predicted relationships to actual clinical outcomes. For example,

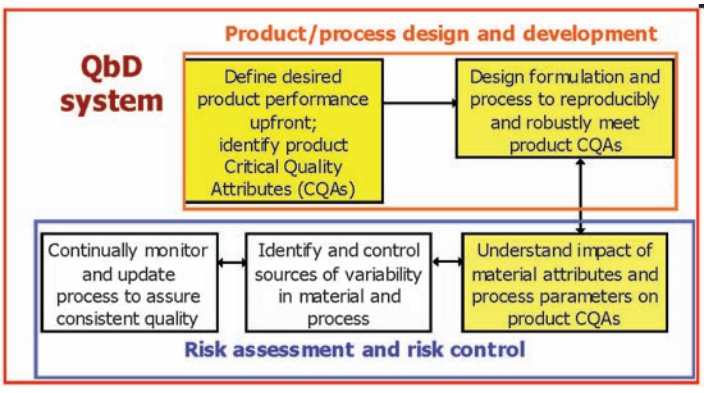

Figure 2. *The QbD System.*

let's assume that a product has a targeted release profile of 40 days. PK models can be developed and the product population distribution of concentration/time relationships generated on the basis of PK data in a patient population. By linking the kinetic and dynamic responses in the patient population, the predicted therapeutic outcomes for any given set of release characteristics can be modeled, and the change in responses with altered *in vivo* release characteristics simulated. This portion of the paradigm is similar to clinical trial simulation, but here the focus is on describing the optimal drug delivery rate (both *in vitro* and *in vivo*) and extent of the uptake of the dose. Once intended release characteristics are determined for a particular formulation, key aspects of *in vitro* product release for acceptance criteria may be identified.

It should be noted that, for example, in the case of antimicrobials, this relationship may be a specific parameter (e.g., time above the minimum inhibitory concentration or the evaluation of partial AUCs versus some targeted response). Or, as previously mentioned, it might be the time to peak concentrations (e.g., hypnotics). Therefore, there is a range of types of correlations that may be appropriate to consider when establishing "clinical relevance."

The question is how can one begin to develop these models and apply the information gathered during product development? How would one need to factor this objective in the clinical trial study design? How can one design a clinical trial to capture the variability in *in vivo* product performance within a patient population and the influence of such variability on clinical outcomes? How can one use such information and models to target an appropriate relationship between dose and the characteristics of target tissue exposure?

Dr. William Jusko will describe issues and complexities associated with the development of PK/PD models and how such models can be used to explore the relationship between *in vivo* drug release and therapeutic response (7). Dr. Jeffrey Barrett will describe the use of modeling and simulation to target dosing strategies and predict optimal *in vivo* product release characteristics in a pediatric population. Discussions will include his recent work on the development of an *in silico* child, and how such models can be used to explore "what if" scenarios with respect to the therapeutic impact of varying *in vivo* product release characteristics (8).

Dr. Roger Jelliffe will describe the development of population PK models from patients, and how one can develop maximally precise dosage regimens to hit the targeted therapeutic goals using nonparametric population models and multiple model dosage design (9). Finally, Dr. Maria Cruanes will present a product development case study using quality target product profile and risk assessment for identifying critical dissolution/release characteristics.

The session will conclude with the all-important roundtable discussion where the potential integration of the presented information, the applicability of the paradigm in Figure 1, and the

benefits and challenges associated with this approach can be explored. In this regard, points to consider include

- How would we adjust (or not) clinical trial designs if we were to attempt to incorporate clinically derived PK/PD data into this model-building process?
- How and when would such data be merged with drug dissolution/release information? Before Phase II a or b?
- How would it affect product labels?
- How could such information influence drug product specifications and the development of design space?

This challenging issue reflects uncharted territory. However, in light of evolving pharmaceutical innovations, answers to these questions and issues are of enormous importance. This workshop will be an important component of a continuing effort to ensure our ability to define and control the critical parameters governing *in vivo* product performance.

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Recent Diversified Inventions

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This report describes certain notable patents recently issued by the U.S. Patent and Trademark Office. It mainly covers patents in the pharmaceutical and drug delivery areas.

Channeled Biomedical Foams and Method for Producing Same (Brown et al.; Ethicon, Inc., U.S.A.) U.S. Patent 7,674,408

This intriguing patent discloses a process for making biomedical, biocompatible scaffolds suitable for use in the repair and regeneration of tissue. The disclosed invention encompasses preparation of a homogenous mixture comprising a synthetic, biocompatible polymer, a solvent in which the polymer is soluble, and a non-solvent in which the polymer is not soluble, wherein the solvent and non-solvent are miscible and the freezing point of the non-solvent is higher than the freezing point of the solvent. Further it involves placing the homogenous mixture in a mold or other device suitable for preparing foam scaffolds for use in repair and regeneration of tissue; cooling the mixture to a first temperature effective to freeze the non-solvent; maintaining the first temperature for a sufficient period of time to allow phase separation of the non-solvent from the homogenous mixture and to generate dendritic crystals; cooling the homogenous mixture to a second temperature sufficient to form a solid; and removing the solvent and non-solvent from the solid to provide a biocompatible, porous foam scaffold that comprises a network of branched channels.

Cosmetic or Pharmaceutical Composition Comprising Peptides, Uses, and Treatment Process (Dal Farra et al.; ISP Investments Inc., U.S.A.) U.S. Patent 7,647,451

The inventors claim to have succeeded in selecting particular substances presenting remarkable properties when they are applied to the skin and to have discovered that peptides corresponding to the general formula (I): (AA)n-Arg-Gly-Ser-(AA)n (I), in which (AA) is an unspecified amino acid, or one of its derivatives, and N is an integer ranging between 0 and 3 have remarkable properties as a skin care agent. The active ingredient is said to have remarkable effects on the skin and a true stimulating and revitalizing action on the skin and cells that compose it. The subject compound is said to have slimming, anti-cellulite properties and protective properties and a very effective action in the fight against the manifestations of cutaneous aging. Further, it is said to have been discovered that the subject peptide has an effect on the modulation of ATP concentration in the cell, intracellular calcium concentration, and production and activation of proteins that are essential to the skin.

Tumor Necrosis Factor Combined with Interferon in Demyelinating Diseases (de Luca et al.; Ares Trading SA, Switzerland) U.S. Patent 7,674,453

The invention disclosed in this patent is said to be based on the finding that the administration of tumor necrosis factor (TNF) in combination with an interferon (IFN) has a beneficial effect on remyelination and significantly reduces clinical signs of multiple sclerosis. It was found that the TNF potentiates the therapeutic effect of IFN in multiple sclerosis. It was further shown that interferon exerts its beneficial effect at sub-therapeutic dosage when administered in combination with TNF. One object of the invention is to use an agent having, stimulating, or maintaining TNF activity in combination with an IFN or an isoform, mutein, fused protein, functional derivative, active fraction, or salt thereof for the manufacture of a medicament for treatment and/or prevention of a demyelinating disease, for simultaneous, sequential, or separate use. Another object of the invention is to provide for a pharmaceutical composition containing an agent having, stimulating, or maintaining TNF activity in combination with an effective amount of an IFN in the presence of one or more pharmaceutically acceptable excipients.

Methods for Enhancing Neuroprotection via Administration of Stem Cells and Blood Brain Barrier Permeabilizers (Borlongan et al.; University of South Florida, U.S.A.) U.S. Patent 7,674,457

This invention is said to provide methods and compositions to enhance the neuroprotective effects of stem cell treatment in a neurodegenerative disorder. In this regard, the invention fulfills in part the need to identify new, unique methods for treating cerebral ischemia. In one embodiment, the method administers cells obtained from umbilical cord blood to an individual in need of treatment, wherein the cells are administered systemically to the individual and a blood brain barrier permeabilizer is co-administered with the cells. In one embodiment, the cells obtained from human umbilical cord blood comprise a volume-reduced cord-blood sample. In a further embodiment, the cells obtained from human umbilical cord blood contain an effective amount of a mononucleated cell. Other embodiments are said to include a composition for the treatment of the neurodegenerative disorder, ischemia, and, preferably, a cerebral infarct. In one embodiment, the composition contains effective amounts of cell obtained from umbilical cord blood and blood brain barrier permeabilizer. In a further embodiment, the umbilical cord-blood cell is a human umbilical cord-blood cell. In one embodiment, the cells obtained from human umbilical cord blood comprise a volume-reduced cord-blood sample.

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Topical Composition, Topical Composition Precursor, and Methods for Manufacturing and Using (Roszell et al.; Skinvisible Pharmaceuticals, Inc., U.S.A.) U.S. Patent 7,674,471

This invention is directed to applications with a topical composition or delivery system when used to promote the delivery of active ingredients to skin tissue. It has an ability to adhere or bind to skin tissue and thereby hold active ingredients in proximity to skin tissue. Active ingredients that can be used include natural and synthetic substances, including medicines, drugs, or other substances. The topical composition precursor of the invention can be provided as a result of melt processing hydrophobic and hydrophilic polymer compositions in the presence of less than ≈1 wt % water. The hydrophobic polymer composition includes a poly(vinylpyrrolidone/alkylene) polymer, wherein the alkylene group contains at least ≈10 carbon atoms. The hydrophilic polymer composition includes at least one hydrophilic polymer containing repeating carboxylic acid groups and/or repeating hydroxyl groups. Exemplary hydrophilic polymers include polyacrylic acid with an average molecular weight of at least ≈50,000 and exhibiting <1% cross-linking, poly(maleic acid/methylvinylether) copolymer with an average molecular weight of at least ≈50,000, starch, derivatives of starch, cellulose, derivatives of cellulose, carboxymethyl cellulose, polyvinyl alcohol, cyclodextrins, dextrans, and mixtures thereof. The hydrophilic polymer composition can include polyacrylic acid with an average molecular weight of between ≈50,000 and ≈4,000,000 and exhibiting <1% cross-linking and/or poly(maleic acid/methylvinylether) copolymer with an average molecular weight of between ≈50,000 and ≈4,000,000.

Anti-microbial Composition (Falder et al.; Byotrol PLC, U.K.) U.S. Patent 7,674,473

According to an aspect of this invention, there is provided an anti-microbial composition containing 1) a first compound with a high surface tension of from 20 to 35 mN/m; 2) a second compound with a low surface tension of from 8 to 14 mN/m; 3) a first anti-microbial agent; and 4) a polar solvent, wherein the composition acts substantially to prevent the formation of microbial colonies on or at a surface of the composition. The anti-microbial composition of the invention is highly effective and works with a broad range of microorganisms. It seems that the anti-microbial composition of the invention works by providing a surface to which microorganisms are substantially prevented from adhering and attaching. In other words, the composition of the invention substantially prevents the occurrence of stage 1 of the biofilm formation process. This means that the microorganisms cannot then multiply and form biofilms.

Endoparasiticidal Gel Composition (Sabnis et al.; Wyeth LLC, U.S.A.) U.S. Patent 7,674,475

The invention disclosed in this patent provides an endoparasiticidal gel composition that contains ≈1.0–3.5% (wt/wt) of moxidectin, ≈10.0–5.0% (wt/wt) of praziquantel, ≈4.0–24.0% (wt/wt) of benzyl alcohol, ≈1.0–34.0% (wt/wt) of ethanol, ≈2.0–15.0% (wt/wt) colloidal silicon dioxide, ≈1.0–20.0% (wt/wt) surfactant, and ≈35.0–61.0% (wt/wt) of an oil. It further provides for a method for the treatment and control of endoparasiticidal infection and infestation in a homeothermic animal and a method for the preparation of an endoparasiticidal gel composition.

Polymer Micelle as Monolayer or Layer-laminated Surface (Kataoka et al.; Johnson & Johnson Vision Care, Inc., U.S.A.) U.S. Patent 7,674,478

The invention is directed toward a coated support surface application, such as a biomedical device, wherein the coating comprises at least one polymeric micelle immobilized on the surface of the biomedical device, the micelle having either a hydrophilic outer shell and hydrophobic inner core or a hydrophobic outer shell and hydrophilic inner core and being composed of a block copolymer with a HLB value ranging from ≈1 to ≈40. The polymer micelle used to coat the support surface may be present as a monolayer. Alternatively, they may be multilayers in which the various layers are crosslinked to each other. In another embodiment, the multilayer micelle contains at least two polymer micelles sandwiching either a high molecular weight polymer compound with a number of functional groups or a multi-functional low molecular weight polymer compound with at least two functional groups.

Polymer Sustained Release Bupropion and Bupropion/Mecamylamine Tablets (Zerbe et al.; Intelgenx Corp., U.S.A.) U.S. Patent 7,674,479

This patent discloses an alternative solution to providing sustained release of bupropion hydrochloride in a tablet dosage form. In accordance with the invention, sustained release bupropion hydrochloride granulation is distributed in a sustained release matrix. More particularly, the pharmaceutical tablets, in accordance with this aspect of the invention, comprise a granular phase composed of bupropion hydrochloride and a hydroxyalkylcellulose. The granular phase is distributed within an extragranular phase containing a particulate material that provides a sustained release effect, such as by providing a diffusion barrier and/or controlled erosion. The formed tablet optionally then is provided with a means to obtain the delayed release of an active, such as an enteric coating.

Rapidly Expanding Composition for Gastric Retention and Controlled Release of Therapeutic Agents, and Dosage Forms Including the Composition (Fleshner-Barak et al.; Teva Pharmaceutical Industries Ltd., U.S.A.) U.S. Patent 7,674,480

In this patent the inventors discovered a composition that expands rapidly in the gastric juices of a patient, thereby increasing the likelihood that the composition will be retained in the stomach for a prolonged period of time. The composition is a blend of a superdisintegrant, tannic acid, and one or more hydrogels and is useful in gastric retention dosage forms because it increases the likelihood that an active ingredient carried by the form will be released in the stomach. A dosage form of the

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invention expands rapidly because it does not contain a superporous hydrogel. The invention is also said to provide a pharmaceutical composition for use in an orally administered pharmaceutical product that expands upon contact with gastric fluid to promote retention of a dosage form in the patient's stomach. The composition comprises a non-hydrated hydrogel, superdisintegrant, and tannic acid, preferably in amounts, exclusive of any other excipients that may be present, of from ≈20 to ≈70 wt % hydrogel, from ≈10 to ≈75 wt % superdisintegrant, and from ≈2 to ≈12 wt % tannic acid.

External Composition Comprising an Aqueous Extract of Red Vine Leaves and an Anti-inflammatory Agent (Matsuda et al.; Boehringer Ingelheim International GmbH, Germany) U.S. Patent 7,674,488

According to this patent, surprisingly, anti-inflammatory and anti-edematous action is found by combining an anti-inflammatory agent with an aqueous extract of red vine leaves. Moreover, a composition of mild anti-inflammatory agents resulted in a safe composition whose efficacy is potentiated for preventing and alleviating discomfort relating to mild to moderate chronic venous insufficiency of the legs with minimum or no adverse reactions. The composition of this interesting invention comprise an anti-inflammatory agent and aqueous extract of red vine leaves.

Multi-phase, Multi-compartment Capsular Delivery Apparatus and Methods for Using Same (Fred H. Miller; Innercap Technologies, Inc., U.S.A.) U.S. Patent 7,670,612 B2

This invention provides novel integrated capsule delivery apparatus and methods for delivering one or more active ingredients or medicaments (e.g., pharmaceutical, biotechnical, nutraceutical, vitamin, dietary supplement, mineral, or combination thereof) in the form of a single-dosage, multi-compartment capsule with one or more active ingredients in a primary capsule and one or more active ingredients introduced into a secondary smaller capsule with a size sufficient to be selectively positionable within the primary capsule, wherein the active ingredient(s) within the primary capsule has a physical state (e.g., solid, liquid, gas, or dispersion) that is different from the physical state of the active ingredient(s) in the secondary capsule. It is an additional objective of this invention to provide novel integrated capsule delivery apparatus and methods for delivering one or more active ingredients or medicaments (e.g., pharmaceutical, biotechnical, nutraceutical, vitamin, dietary supplement, mineral, or combination thereof) in the form of a single-dosage, multi-compartment capsule with one or more active ingredients in a primary capsule and the same active ingredient(s) introduced into a smaller secondary capsule with a size sufficient for to be positionable within the primary capsule, wherein the active ingredient(s) in the primary capsule has a physical state (e.g., solid, liquid, gas, or dispersion) that is different from the active ingredient(s) in the secondary capsule.

Traditional Chinese Medicine Composition to Treat Rheumatoid Arthritis and Preparation Method Thereof (Guo et al.) U.S. Patent 7,662,412 B2

The invention discloses a traditional Chinese medicine composition to treat rheumatoid arthritis and its preparation method. The composition is mainly composed of the following crude drugs: ant, radix salviae miltiorrhizae, radix aconiti preparata, radix ginseng, caulis spatholobi, ramulus cinnamomi, etc. According to pharmaceutical methods, various clinically acceptable dosage forms can be prepared from the composition of this invention, including, but not limited to, one of the following dosage forms: tablets, capsules, pills, granules, suspension, dripping pills, oral liquid preparation, etc. The drug in this invention has the functions of invigorating the kidney and spleen, promoting blood flow and clearing out the veins, expelling wind-evil and removing wetness, and eliminating cold to stop pain. It can be effectively used in the treatment of lingering arthralgia with weakness, arthralgia, intumesce, and morning stiffness, numbness, and stickiness, difficulty flexing and extending, rigor and deformation, rheumatism, and rheumatoid arthritis with the above symptoms. ■

Welcome New Members

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CRS Delivering Bioactives

In the News

Compiled by Steven Giannos
Industrial Editor

March 2010

Emisphere Technologies and Alchemia to Research an Oral Formulation of Fondaparinux with Eligen® Technology

Business Wire: March 18, 2010 – CEDAR KNOLLS, NJ, and BRISBANE, AUSTRALIA – Emisphere Technologies, Inc. (OTCBB: EMIS) and Alchemia Ltd. (ASX: ACL) have announced that they are joining efforts to develop an oral formulation of the anti-coagulant drug fondaparinux with Emisphere's Eligen® technology.

Emisphere's broad-based drug delivery platform, known as Eligen® technology, uses proprietary, synthetic carriers to enhance the oral bioavailability of a drug without altering its chemical form or biological activity. Fondaparinux, an anti-coagulant used for the prevention of deep vein thrombosis, is marketed in injectable form as Arixtra® by GlaxoSmithKline. Arixtra® has been off patent since 2002, but due to the complexity of its synthesis, there is currently no approved generic or alternative source of commercial-scale active pharmaceutical ingredient. Alchemia has developed a novel, patent-protected synthesis for the manufacture of fondaparinux at commercial scale. In March 2009, Alchemia's manufacturing and U.S. marketing partner, Dr. Reddy's Laboratories (NYSE: RDY) submitted an ANDA to the U.S. FDA for a generic version of the injectable form of fondaparinux.

"An oral formulation of fondaparinux could dramatically increase the market potential for fondaparinux. Based on what we know from our experience with other chemically related anti-coagulants, the profile of fondaparinux should fit very well with the Eligen® Technology given its half life and safety profile. Although developing an oral formulation of an injectable compound is always challenging, this project could produce substantial benefits for the medical community. The combination of Emisphere's delivery technology and Alchemia's fondaparinux may ultimately allow us to bring an oral anti-coagulant to market in an accelerated fashion," said Michael Novinski, president and CEO of Emisphere Technologies.

"We have already seen preclinical data suggesting that enhanced levels of oral absorption can be achieved for fondaparinux. If we can successfully optimize the dose formulated with the Eligen® Technology from Emisphere it would open up a host of medically and commercially compelling opportunities for fondaparinux," said Pete Smith, CEO of Alchemia Ltd. "We will initially evaluate a number of different formulations in order to optimize oral bioavailability and pharmacokinetics, with the aim of then rapidly moving into human clinical studies."

Zogenix Initiates Pivotal Phase III Clinical Trial for Novel Formulation of Oral Controlled-Release Hydrocodone

PRNewswire: March 17, 2010 – SAN DIEGO, CA – Zogenix, Inc., a privately held pharmaceutical company, has announced that it has initiated a pivotal Phase III clinical trial with ZX002, a novel, oral controlled-release formulation of hydrocodone without acetaminophen. ZX002 is being developed for the treatment of moderate to severe pain in individuals who require around-the-clock opioid therapy for the control of pain. Hydrocodone is the most widely prescribed drug in the United States, but there are currently no products available with only hydrocodone or with controlled-release formulations. ZX002, which incorporates Elan's proprietary SODAS® technology, offers a unique controlled-release profile that utilizes both immediate and extended release properties designed to enable twice daily dosing.

"We are pleased to be initiating this pivotal Phase 3 trial of ZX002 as the first single-entity, controlled-release hydrocodone formulation," said Cynthia Robinson, Ph.D., chief development officer of Zogenix. "We believe this hydrocodone therapy could offer significant benefits to both the patient and the practicing physician by allowing for less frequent dosing with a customized controlled-release profile and the ability to titrate to higher hydrocodone doses than currently recommended for hydrocodone products burdened by combination formulations. Further, we believe ZX002 may offer patients an option for the treatment of their chronic pain that potentially avoids some of the serious side effects that can accompany chronic use of combination opioids that contain acetaminophen, or other non-steroidal anti-inflammatory drugs (NSAIDs)."

This Phase III efficacy trial is designed to enroll approximately 600 patients with chronic low back pain. The trial is a United States-based multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of ZX002. For further information regarding this study, visit www.clinicaltrials.gov and reference NCT01081912.

Quinnova Pharmaceuticals Launches Neosalus Cream Using Proderm Technology

Business Wire: March 16, 2010 – NEWTOWN, PA – Quinnova Pharmaceuticals, Inc., a specialty pharmaceutical company that develops and markets novel topical delivery platform-based prescription drugs, has launched its Neosalus cream. Neosalus cream, the latest addition to Quinnova's Neosalus brand, is a prescription product with anti-inflammatory properties that can be used without age or long-term use restrictions for the treatment of a variety of chronic inflammatory skin conditions like atopic dermatitis, contact dermatitis, and hand eczema. The non-irritating cream is gentle,

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safe, and fragrance- and alcohol-free. Using the Proderm technology delivery system, Neosalus cream complements Quinnova's Neosalus product line.

"I routinely use Neosalus in my dermatology office," stated Firas Hougeir, M.D. "I appreciate the versatility of the product and being able to choose between the foam and the cream for my patients. The cosmetic characteristics of the product have led to better patient compliance and treatment outcomes. Neosalus has been a strong addition to my armamentarium, allowing me to decrease steroid use in my patients and increase their tolerance of potentially irritating treatment regimens."

Neosalus repairs, protects, and hydrates the skin. Neosalus cream restores dysfunctional skin by replenishing lost physiological lipids, functions as a protectant to reduce the penetration of irritants, and improves skin hydration. Patients with chronic inflammatory skin conditions often experience dry, itchy, and scaly skin, with compromised skin barrier decreasing protection against irritants and infection. These disorders are characterized by cycles of exacerbations and remissions. Neosalus' anti-inflammatory properties help reduce the frequency and severity of flare-ups, decrease reliance on corticosteroids, and complement other simultaneous treatments.

The cosmetically elegant, non-comedogenic Neosalus cream has been formulated for easier application to smaller surface areas, like the face, and targeted application on other body areas, while the earlier launched Neosalus foam is suited for application to larger body areas.

"We're pleased to offer the Neosalus Cream as a significant addition to the treatment options for chronic inflammatory skin disorders," said Jeffrey S. Day, founder, president, and CEO of Quinnova Pharmaceuticals. "Clinicians, in general, are dissatisfied with current topical treatment options for chronic skin conditions, often citing poor efficacy and low patient compliance. We developed the Neosalus Cream in order to cater to the specific needs of our doctors and their patients, realizing the necessity of providing a safe, effective, and more convenient offering for atopic dermatitis and hand eczema patients."

Many products that treat chronic inflammatory skin conditions are alcohol-based, which can lead to more irritation and poor patient compliance. Proderm technology, on the other hand, is composed of a mixture of water and lipids and does not contain alcohol. Proderm is effective because of its ability to protect, repair, and hydrate the skin with its ease of application and rapid absorption. It protects against external irritants by forming a physical barrier, facilitates the repair of the skin by providing essential nourishment in the form of free fatty acids, and hydrates the skin. Proderm is fragrance-free, non-comedogenic, non-alcohol based, and non-greasy.

SCOLR Pharma Acquires the Rights to Nuprin® from CVS

PRNewswire: March 16, 2010 – BOTHELL, WA – SCOLR Pharma, Inc. (NYSE AMEX: DDD) announced that it has acquired rights to the Nuprin® name in connection with sales of ibuprofen. SCOLR paid $180,000 to purchase all rights, titles, and interests of Advanced Healthcare Distributors, LLC (an affiliate of CVS Caremark Corporation) to the Nuprin® name, including its portfolio of global registrations (exclusive of Canada).

Stephen J. Turner, SCOLR Pharma president and CEO, said, "Our acquisition of this globally recognized name will provide us with additional opportunities for ibuprofen-based products. We expect that the acquisition will allow us to generate potential near-term sales of immediate release 200 mg ibuprofen tablets, in addition to providing us with enhanced options on our extended release ibuprofen program."

Ranbaxy Announces Settlement of Actos® (Pioglitazone Hydrochloride) Patent Litigation

PRNewswire: March 15, 2010 – JACKSONVILLE, FL – Ranbaxy Laboratories Limited (RLL), along with its wholly owned subsidiary Ranbaxy Pharmaceuticals Inc. (RPI), has announced that they have reached an agreement with Takeda Pharmaceutical Company Limited and Takeda Pharmaceuticals North America resolving outstanding patent litigation related to Ranbaxy's generic equivalent version of Actos® (pioglitazone hydrochloride) 15-, 30-, and 45-mg tablets. Under the terms of the agreement, Takeda granted Ranbaxy a non-exclusive royalty-free license to its U.S. patents covering Actos®. Under the terms of the agreement, Ranbaxy has certainty in the launch of its generic equivalent formulation of Actos® on August 17, 2012, or earlier under certain circumstances.

Actos® had approximately $3.4 billion in brand sales for the 12 months ending December 31, 2009, according to IMS Health. Actos® is a once-daily oral prescription medication that, with diet and exercise, has been shown to be effective for the treatment of type 2 diabetes. "This agreement will allow RPI to bring to patients with diabetes a generic alternative in this important therapeutic area," according to Jim Meehan, vice president of sales and distribution for RPI.

RPI, based in Jacksonville, Florida, is a wholly owned subsidiary of RLL, India's largest pharmaceutical company. RPI is engaged in the sale and distribution of generic and branded prescription products in the U.S. healthcare system. The company's foray into novel drug delivery systems has led to proprietary platform technologies, resulting in a number of products under development. Ranbaxy is a member of the Daiichi Sankyo Group. Daiichi Sankyo is a leading global pharma innovator, headquartered in Tokyo, Japan. Actos® is a registered trademark of Takeda Chemical Industries, Ltd.

FDA Allows IND for Bio-Path Holdings' Liposomal Grb-2

Business Wire: March 12, 2010 – HOUSTON, TX – Bio-Path Holdings, Inc. (OTCBB: BPTH), a publicly traded biotechnology company with drug development operations in

Houston, TX, has announced that the U.S. FDA has allowed an IND (investigational new drug) for the company's lead cancer drug candidate liposomal Grb-2 to proceed into clinical trials. The IND review process was performed by the FDA's Division of Oncology Products and involved a comprehensive review of data submitted by the company covering pre-clinical studies, safety, chemistry, manufacturing and controls, and the protocol for the Phase I clinical trial.

Bio-Path is developing a neutral lipid-based liposome delivery technology for nucleic acid cancer drugs (including antisense and siRNA molecules). The company's drug candidate liposomal Grb-2 (BP-100-1.01) is an antisense drug substance targeted to treat several types of cancer. The FDA's clearance of the IND allows Bio-Path to proceed with a Phase I clinical trial in patients with chronic myelogenous leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, and myelodysplastic syndrome. Commencement of the trial will occur after patients are enrolled and administrative details are finalized. The company does not expect significant delays for these steps.

Peter Nielsen, president and CEO of Bio-Path Holdings, Inc., commented, "The granting of the IND represents a major milestone in the development of Bio-Path Holdings. As of today, Bio-Path has made the transition from a pre-clinical to a clinical-stage company. We look forward to commencing the Phase I clinical trial of liposomal Grb-2 and demonstrating the safety and effectiveness of Bio-Path's neutral lipid delivery technology."

Access Pharmaceuticals Reports Significant Oral Bioavailability of Cobalamin Oral Insulin in Additional Studies

PRNewswire: March 11, 2010 – DALLAS, TX – Access Pharmaceuticals, Inc. (OTCBB: ACCP) has received reports of significant bioavailability of orally delivered insulin in two independently conducted animal studies. The studies, which confirm earlier findings, were performed as part of ongoing work with commercial collaborators who are evaluating Access' Cobalamin oral drug delivery technology.

Access previously reported that its novel Cobalamin-coated insulin-containing nanoparticle formulations delivered orally provided a pharmacological response (lowering of blood glucose levels in animal models) equivalent to >80% of that achieved by insulin delivered subcutaneously. The company believes the substantial oral bioavailability underscores the formulation's potential for clinical development and ultimate commercialization. Additionally, Access believes that its Cobalamin oral drug delivery technology has broad applications to proteins, small molecule drugs, hormones, and potentially sRNAi therapeutics.

In addition to insulin, adaptation of this technology has provided a Cobalamin human growth hormone (HGH) formulation that has demonstrated good efficacy, represented by >25% improvement in weight gain, when given orally in an established animal model. Access continues moving its insulin and HGH products toward clinical development, while submitting additional patents surrounding both formulations. "We remain excited about the potential of our Cobalamin oral drug delivery technology, and the positive data being generated," stated Jeff Davis, CEO of Access Pharmaceuticals, Inc.

Access' worldwide exclusive patented Cobalamin technology utilizes the body's natural vitamin B_{12} oral uptake to facilitate oral absorption of pharmaceuticals by a "Trojan Horse" mechanism. This technology platform provides Access with the ability to develop a number of different formulations with improved benefits for various disease applications. "We have several ongoing discussions with other companies regarding the application of our oral drug delivery options for their promising new drugs. Additionally, we continue exploring ways to move this to a proof-of-concept human trial as quickly as possible," commented Phillip Wise, Access vice president of business development and strategy.

Access Pharmaceuticals, Inc. is an emerging biopharmaceutical company that develops and commercializes proprietary products for the treatment and supportive care of cancer patients. Access' products include ProLindac, currently in Phase II clinical testing of patients with ovarian cancer, and MuGard, for the management of patients with mucositis. The company also has other advanced drug delivery technologies, including Cobalamin-mediated targeted and oral drug delivery, its proprietary nanopolymer delivery technology based on the natural vitamin B_{12} uptake mechanism and thiarabine, a new generation nucleoside analog that has demonstrated both pre-clinical and clinical activity in certain cancers. For additional information, visit www.accesspharma.com.

Watson Announces Agreement to Acquire U.S. Rights to Columbia Laboratories, Inc.'s Crinone® Progesterone Gel Product Line

PRNewswire: March 4, 2010 – MORRISTOWN, NJ – Watson Pharmaceuticals, Inc. (NYSE: WPI) has announced an agreement to expand their women's health brand product portfolio with the acquisition of the exclusive U.S. rights to Columbia Laboratories, Inc.'s bioadhesive progesterone gel products currently marketed under the trade names Crinone® and Prochieve® for the treatment of infertility and secondary amenorrhea. The two companies will collaborate in the ongoing Phase III development program toward a new indication for these products for the prevention of preterm birth in women with a short cervix, as well as a global development program for second-generation products for this indication and infertility. Watson will also acquire 11.2 million shares of Columbia common stock.

The acquisition is subject to customary closing conditions, including the approval of Columbia's stockholders. The closing of the acquisition is expected to occur in the second quarter of 2010. After the close of the acquisition, Watson intends to

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immediately begin marketing Crinone® and Prochieve® in the United States to reproductive endocrinologists and ob/gyns through the existing brand sales forces.

"The addition of Crinone® and Prochieve® demonstrates our commitment to expand our emerging position in distinctive women's healthcare products. It builds on a portfolio of products used by the ob/gyn that currently includes our Gelnique® (oxybutynin chloride) gel treatment for overactive bladder (OAB) and Femring® (estradiol acetate) vaginal ring hormone replacement therapy. It also provides a stronger market foundation for the portfolio of women's health products in development, including Uracyst®, under development for cystitis, a new emergency contraceptive, a novel oral contraceptive and two additional unique contraceptives currently in Phase 3," said Paul Bisaro, Watson president and CEO. "Crinone® has a proven record in infertility, and we are confident in our ability to expand its acceptance using our specialty ob/gyn sales team. In addition, if we are successful in receiving FDA approval for a new preterm birth indication, we will have the opportunity to create a new market and address a significant and unmet medical need."

Crinone® is currently used for progesterone supplementation or replacement as part of an assisted reproductive technology (ART) treatment for infertile women with a progesterone deficiency. Patient preference for Crinone® has been demonstrated in five clinical trials. The product is also available under the trade name Prochieve®.

A Phase III clinical program is currently underway in collaboration with the National Institutes of Health (NIH) to evaluate the safety and efficacy of Prochieve® for the prevention of preterm birth in women with a short cervix. Preterm birth occurs in one in every eight live born infants, and short cervix is the single most important predictor of preterm birth. There are currently no products approved for the prevention of preterm birth.

Archimedes Pharma Announces Major Fund Raising of £65 Million

PRNewswire: March 2, 2010 – READING, ENGLAND – Archimedes Pharma, a leading specialty pharma company, has raised £65 million (approximately US$100 million) in new funding. The round was led by new investor Novo Growth Equity, the growth equity fund of Novo A/S, and included participation by major current investor Warburg Pincus, a global private equity firm. Archimedes also announced the appointment of new President and CEO Jeffrey H. Buchalter, formerly president and CEO of United States-based Enzon.

The funds will be used to establish Archimedes' operations in the United States and support the growth of the successful specialty pharma business in Europe. The funds will also be used to support the global commercial launch of PecFent (previously known as NasalFent), Archimedes' innovative, simple-to-use, fentanyl nasal spray for the treatment of breakthrough cancer pain. PecFent has been filed for approval in Europe and the United States and is expected to be approved for commercial sale in both regions during 2010. PecFent is supported by an extensive Phase III clinical development program in which the product met all primary and secondary end-points. Crucially, the Phase III studies demonstrated that PecFent showed onset of pain relief within 5 min of dosing, statistically significant improvements in pain relief versus immediate release morphine, together with high levels of patient acceptability and consistent effectiveness in use.

Simon Turton, managing director of Warburg Pincus, said, "We have supported Archimedes since its foundation in 2004 and are delighted to invest again in such an exceptional company as it enters a new stage in its growth. We are particularly pleased to welcome Jeff as President and CEO and to the Board of Archimedes. His vast experience and knowledge of the pharmaceutical industry, and specifically oncology, will be instrumental in accelerating the Company's success through an international platform. This major injection of funding and the appointment of Jeff as the new President and CEO mark the beginning of a new phase in Archimedes' growth plans."

Ulrik Spork, managing partner of Novo Growth Equity, said, "We have been impressed with the successful track record of Archimedes over the last five years, and are very pleased to contribute to the further transformation of the Company with the launch of PecFent…. Archimedes represents an ideal investment opportunity for us and supports our strategy to take major stakes in promising late stage life sciences companies with near-term commercial potential."

Jeffrey H. Buchalter, president and CEO of Archimedes, commented, "Archimedes is at a transformational stage in its development. It has built up a successful specialty pharma business in Europe and has filed its lead product, PecFent, for product approval in both Europe and the US. I am delighted to join as President and CEO to accelerate the expansion of Archimedes' business in Europe, support the commercialisation of PecFent, and build the operations in the US market."

The board of Archimedes will now include Simon Turton and Piyush Shukla of Warburg Pincus; Ulrik Spork and Goran Ando of Novo A/S; and Jeffrey H. Buchalter. Archimedes Pharma is a specialty pharmaceutical company marketing and selling an expanding portfolio of specialist products to hospital-based prescribers in Europe. Focused on the oncology, pain, neurology, and critical care sectors, Archimedes currently markets a range of products in the United Kingdom, France, Germany, and Ireland and will continue to expand its commercial presence in Spain and the United States during 2010.

In Europe by Archimedes currently markets Gliadel, a biodegradable wafer impregnated with carmustine for high-grade glioma; Zomorph, an oral sustained release morphine product for moderate to severe pain, particularly cancer pain; Oramorph, a liquid immediate release morphine product also indicated for moderate to severe pain; Apomorphine injection for motor fluctuations in advanced Parkinson's disease; and Pabrinex, a high-potency vitamin formulation used to treat the

symptoms of malnutrition, especially in patients with alcohol misuse problems. Archimedes is also developing a robust, high-value pipeline of in-house products in pain, Parkinson's disease, and critical care. It applies its drug delivery technologies to proven molecules that have yet to achieve their market potential due to their current mode of delivery. This approach reduces the company's development risk, while delivering significant clinical and commercial benefits.

Archimedes submitted a centralized Marketing Authorization application with the European Medicines Agency for PecFent in April 2009 and submitted a New Drug Application with the U.S. FDA in August 2009. The product is expected to be approved for commercial sale during 2010 in both territories. Archimedes' transformational product, PecFent, is an innovative and highly differentiated fentanyl citrate nasal spray, for the rapid relief of breakthrough cancer pain, based on Archimedes' PecSys™ technology. Phase III data illustrates that PecFent has a potential best-in-class profile among fentanyl products for breakthrough cancer pain and is the first product to demonstrate onset of pain relief within 5 min of dosing.

The PecFent aqueous solution has a low viscosity and is easily delivered in a low volume of 100 µL using a nasal spray pump. The pump produces a fine mist of similarly sized spray droplets that are deposited into the front of the nostril. The calcium ions present on the nasal mucosa cause the pectin to form a thin gel layer, which allows fentanyl to be retained on the nasal mucosa, allowing a rapid but controlled absorption into the systemic circulation. The PecSys™ technology avoids problems associated with simple solutions used in nasal sprays, such as excessive levels of drug and dripping or swallowing of the drug solution.

Archimedes' technologies—ChiSys®, PecSys™, and TARGIT®—are also used in a number of partnered products in late-stage clinical development. ChiSys®, an innovative drug delivery technology that enhances the residence time of molecules on mucosal membranes, has proven potential for vaccine delivery. Pre-clinical and clinical studies of nasally administered vaccines have demonstrated enhanced immune response. PecSys™ is Archimedes' patented drug delivery system, built around its novel pectin technology, designed to maximize the potential of systemically absorbed drugs by enhancing drug performance and improving patient acceptance. For more information, please visit: http://www.archimedespharma.com.

Celsion Plans to Launch Phase II Program to Study ThermoDox in Combination with RFA for Colorectal Liver Metastases

PRNewswire: March 1, 2010 – COLUMBIA, MD – Celsion Corporation (Nasdaq: CLSN) will initiate a randomized Phase II study of lyso-thermosensitive liposomal doxorubicin (ThermoDox) and radiofrequency ablation (RFA) for colorectal liver metastases (CRLM). Dr. Steven K. Libutti, professor and vice chair, Department of Surgery, and director of the Montefiore-Einstein Center for Cancer Care at the Montefiore Medical Center and Albert Einstein College of Medicine in New York, will serve as principal investigator for the study. In addition to Montefiore Medical Center, at least two other leading research institutions from North America and the Asia Pacific region (including Japan) will be included in the Phase II study, which is expected to commence in the second half of 2010. The study is meant to address the growing unmet medical needs of colorectal liver metastases, which is globally prevalent and is currently treated by RFA.

"Celsion Corporation first began studying ThermoDox in combination with RFA for liver metastases in a Phase I safety study of 24 patients, 15 of which had liver metastases from 9 primary sites, including CRLM," said Michael Tardugno, president and CEO of Celsion. "The safety experience and dose response relationship we witnessed in the Phase I study was evident in both primary and metastatic tumors. Building upon this data, we have made the decision to pursue a randomized Phase II study. CRLM is an indication which we believe has a large addressable market, and we expect that CRLM will be a label extension to hepatocellular carcinoma, increasing the value of ThermoDox."

"Having previously studied ThermoDox and completed the Phase I study, I felt the CRLM indication must be further investigated," said Dr. Steven K. Libutti, an expert in treating liver cancer metastases. "There is a large unaddressed population here in North America, and I believe ThermoDox may play a role in treating liver metastases, particularly for larger tumors where survival rates are poor. We believe we are well positioned to conduct this study given the outstanding clinicians and our vast experience in clinical trial research at the Montefiore-Einstein Center for Cancer Care."

February 2010

Echo Therapeutics Announces Completion of Next Generation Electronic Components for Its Revolutionary, Patented Symphony tCGM System

PRNewswire: February 18, 2010 – FRANKLIN, MA – Echo Therapeutics, Inc. (OTCBB: ECTE), a company developing the needle-free Symphony tCGM system as a non-invasive, wireless, transdermal continuous glucose monitoring (tCGM) system and the Prelude SkinPrep system for transdermal drug delivery, has announced that the company has made a significant advance in the product design of its Symphony tCGM device and has developed its next generation electronic component package. This important advance includes an initial 33% reduction in component size and improved architectural design compared to the prototype electronic package of the earlier Symphony tCGM device. The company expects to complete the product development work for the entire Symphony tCGM system in the near future and anticipates entering new clinical trials shortly thereafter.

The completion of this electronic component package represents a major step toward custom integrated circuitry and product

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development completion. The company believes this accomplishment, coupled with the improved, one-piece biosensor that utilizes new materials and an improved geometrical design, will improve sensor performance and significantly decrease the size of the tCGM device. The final Symphony tCGM device is intended to be a cost-effective product that allows for advanced continuous glucose monitoring for patients and healthcare providers.

"The completion of this critical step in the product development program for Symphony demonstrates the Company's steadfast commitment to rapidly developing the world's most advanced solution for needle-free, continuous glucose monitoring technology," stated Patrick T. Mooney, MD, chair and CEO of Echo Therapeutics. "The new electronics and device architecture replace our existing prototype with advanced, efficient and more effective components…. We believe that this technological improvement, combined with our new one-piece biosensor technology, will improve the accuracy of Symphony, while enhancing cost savings in manufacturing through our plans for future custom circuitry integration. Cumulatively, these improvements further strengthen our anticipated competitive position for Symphony in the glucose monitoring market, a $10 billion-plus annual market opportunity. We look forward to testing our commercially ready Symphony tCGM System in a clinical trial in the near term, confirming the performance attributes we have observed in internal testing."

Otonomy Receives FDA Clearance to Initiate Clinical Trial in Patients with Meniere's Disease

PRNewswire: February 17, 2010 – SAN DIEGO, CA – Otonomy, Inc. announced that the U.S. FDA has granted clearance of the company's Investigational New Drug (IND) application for the clinical trial of OTO-104 in patients with Meniere's disease, a debilitating disorder of the inner ear affecting balance and hearing.

The FDA clearance enables Otonomy to move forward with the first clinical trial of a sustained release drug delivered by direct otic injection. Using an approach called intratympanic (IT) injection, otolaryngologists deposit the drug into the middle ear via a small perforation in the tympanic membrane (eardrum). IT drug delivery results in increased drug exposure to the inner ear, where the organs for balance and hearing are located, and minimizes systemic exposure that can cause side effects.

"This marks an important milestone for the company and completes our rapid transition to a clinical-stage organization after less than eighteen months from the start of OTO-104 development," said Jay Lichter, Ph.D., CEO and co-founder of Otonomy. "Furthermore, this advancement demonstrates the utility of our novel, patent-protected formulation approach and enables us to move other development programs toward clinical trials."

The study is a prospective, randomized, placebo-controlled, multicenter, Phase Ib study of OTO-104 given as a single IT injection in subjects with unilateral Meniere's disease. While the primary endpoint of the study is safety and tolerability, a number of efficacy endpoints will be monitored, including the frequency of vertigo attacks experienced by patients pre- and post-treatment.

"Intermittent attacks of vertigo, hearing loss, tinnitus, and aural fullness can be very disruptive and debilitating for Meniere's disease patients," said Jeffrey Harris, M.D., Ph.D., chief of the Division of Otolaryngology-Head & Neck Surgery at University of California San Diego and a co-founder of Otonomy. "Although there are no FDA-approved drug treatments to control these symptoms, IT steroid injections appear to provide relief for many patients as demonstrated in numerous independent physician-sponsored clinical studies."

OTO-104 is a proprietary formulation of the steroid dexamethasone designed to provide sustained drug release to the inner ear from a single IT injection. A key component of this formulation is a thermosensitive gel that increases residence time in the middle ear, thereby enabling higher levels of drug exposure to the inner ear. Preclinical studies confirm the extended release profile of OTO-104 and significant advantage over aqueous formulations that rapidly drain from the middle ear through the Eustachian tube. Sustained release is important to maximize therapeutic effect, enhance drug distribution to the inner ear, and reduce response variability.

Soligenix Announces Issuance of Hong Kong Patent for Its LPM™ Oral Drug Delivery Technology

PRNewswire: February 17, 2010 – PRINCETON, NJ – Soligenix, Inc. (OTCBB: SNGX), a late-stage biotechnology company, has received a Hong Kong patent that addresses its lipid polymer micelle (LPM™) technology for the improved oral delivery of drugs. The issued Hong Kong patent, HK 1071054, entitled "Stabilized Reverse Micelle Compositions and Uses Thereof," covers lipid structures (reverse micelles) that promote the intestinal absorption of peptides and other sensitive drugs that cannot otherwise be given orally.

"The issuance of the Hong Kong patent for LPM™ further demonstrates the novelty of this drug delivery system and the preclinical results clearly show that it is a competitive system for oral delivery of drugs, especially those biotechnology products derived from synthetic peptide chemistry or recombinant DNA," said Christopher J. Schaber, Ph.D., Soligenix president and CEO. "We also believe that the LPM™ system will be applicable to a large number of water-soluble drugs including peptides that are poorly permeable, resulting in increased patient compliance and safety."

The issuance of this patent in Hong Kong follows the issuance of the same patent in Europe in 2009.

Obecure Executes Licensing and Clinical Supply Agreement with Farmaceutici-Formenti SPA for Extended Release Formulation of Betahistine

PRNewswire: February 16, 2010 – RAMAT GAN, ISRAEL – Obecure Ltd. (www.obecure.com), a subsidiary of Bio-Light Israeli Life Science Investments Ltd. (TASE: BOLT), has announced the execution of a licensing and clinical supply agreement with Farmaceutici-Formenti SPA, the Italian Subsidiary of the Grunenthal Group. The agreement extends the 2008 strategic supply agreement between the parties to know-how and patents covering innovative extended release formulations of betahistine dihydrochloride, the active pharmaceutical ingredient of the company's proprietary drug Histalean®. The extended release formulation (XR) allows the drug to achieve greater plasma concentrations for a longer duration and, thus, is likely to improve its beneficial actions.

Histalean® is comprised of betahistine dihydrochloride, a dual-action histamine type H1 receptor agonist and a histamine type H3 negative autoreceptor inhibitor. It is a highly safe generic drug, approved since the 1960s for treatment of Meniere's disease (vertigo) in most countries. In the United States, although its safety was not in doubt, the drug was withdrawn in 1972 for insufficient efficacy in treatment of this disease.

Obecure is focused on development of Histalean® as an adjunctive to antipsychotic drug therapy for improved treatment of schizophrenia, bipolar disorder, and major depression. Obecure has recently announced the outcomes of randomized, placebo controlled Phase Ib and pilot Phase II trials, showing that co-administration of Histalean® with olanzapine (Zyprexa®) safely and significantly reduced weight gain and somnolence, two of the most serious side effects associated with this drug, as with most of the second-generation antipsychotics (SGA) as a drug class, including risperidone (Risperdal®), quetiapine (Seroquel®), and aripiprazole (Abilify®). Interestingly, both side effects are mainly caused by the affinity of these drugs to the histaminic H1 receptor and their inhibition of histaminergic neurotransmission.

Obecure's hypothesis is that Histalean®'s "prohistamine" activity counters SGA's side effects by offsetting their antihistamine action. Indeed, the current clinical trial results suggest that the dose required to effect mitigation of SGA-associated side effects (at least 144 mg/day) may exceed that which is approved for Meniere's disease (48 mg/day). As such high doses have been shown safe, alone and in conjunction with olanzapine, the company has an interest in pursuing the clinical evaluation of innovative high-dose and extended release formulations, as developed by the Grunenthal Italian subsidiary. "This agreement is a major step forward in our effort to develop Histalean® and ensure its benefit to psychiatric patients treated with antipsychotic drugs," said Dr. Yaffa Beck, CEO of Obecure, adding that "It not only assures us a high quality drug manufacturer and supplier of extended release betahistine formulations for our clinical studies, it also enhances the probability of our clinical success, as well as our intellectual property portfolio."

Fulfilling a great and previously untapped market need, the improved tolerability and efficacy of the SGA drugs, was translated to annual sales growth from <$1 billion in 1994 to >$15 billion in 2009. However, in recent years there has been growing concerns of regulators and practitioners about the induction of weight gain by these drugs, reducing patients' compliance and exposing them to metabolic syndrome, diabetes, and cardiovascular disorders; a concern that has resulted in the issuance of black box warnings by the FDA and greatly affected prescription decisions. Moreover, daytime sleepiness (somnolence) induced by these drugs seriously impacts patients' quality of life—prohibiting driving, hampering their ability to hold jobs and/or continue with their education.

According to the terms of the agreement, Grunenthal will supply Obecure with the XR betahistine and matching placebo tablets for use in its upcoming clinical studies and, pending successful clinical outcomes, will exclusively manufacture XR-Histalean® and be entitled to license it for distribution and sale in Italy.

Russia Invests in Cancer Nanodrug Capacity and Safety

In-PharmaTechnologist.com: February 16, 2010 – MOSCOW, RUSSIA – Rusnano, the group set up to promote Russia's nanotechnology infrastructure, says nanodrug development partnership will improve patient access and cut cancer death rates across the country. The project will focus on expanding the production capacity for anticancer agents developed by the Russian Academy of Medical Sciences' NN Blokhin Cancer Research Centre in Moscow using liposomal targeted delivery technology. Rusnano will contribute RUB1.3 billion (€31.6 million), while Novouralsk-based pharma firm Medsintez, which will undertake commercial manufacture of the drugs developed by the Blokhin centre, will invest RUB2.6 billion.

The production of liposome nanotechnology-based versions of doxorubicin, lizomustin, tsifelin, aranoz, and bacteriochlorin, as well as of drugs delivered using immunoliposome and monoclonal antibodies, is slated to begin by 2014. Olga Shpichko, managing director of Rusnano, said, "Production of highly effective anti-cancer drugs in Russia will lower death rates from cancer among all population groups; it will increase the average lifespan and improve the quality of life." Shpichko went on to predict the additional capacity will reduce prices, improve accessibility, and allow the government to increase the amount of drugs it purchases for target programs without changing the budget.

In a separate agreement, Rusnano has teamed up with the Russian Federal Medical Biological Agency (FMBA) to ensure that nanodrugs are made in a way that ensures the "epidemiological well being of the country's inhabitants." Under the agreement, Rusnano and FMBA will develop technical and organizational measures to safeguard production and use of

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nanomaterials, nanotechnology, and products of the nanoindustry. The organizations will also have a role in the creating of laws governing required safety standards for nanodrugs, covering everything from initial development and scientific research to production, consumption and disposal of the products.

Formation of the partnership follows just a few weeks after the United States examined its rules on nanotech drug safety. The proposed laws, the Nanotechnology Safety Act of 2010 , would amend the Federal Food, Drug and Cosmetic Act to establish a nanotechnology safety program at the U.S. FDA.

PARI Pharma Enrolls First Patient in Phase IIb Study of L-CsA

PRNewswire: February 11, 2010 – MONTEREY, CA – PARI Pharma has enrolled the first patient in its Phase IIb clinical trial studying inhaled liposomal cyclosporine A (L-CsA) delivered via a customized investigational eFlow nebulizer system. The multinational study is investigating the safety and efficacy of PARI's L-CsA formulation. In previous clinical trials, reactions from physicians and lung transplant recipients to PARI's drug-device combination were encouraging.

"We are very pleased to move forward with this investigational treatment aimed at preventing bronchiolitis obliterans, which is an incurable small airway disease in lung transplant recipients. This study has been designed with advice from the European Medicines Agency under L-CsA's orphan drug designation status," said Manfred Keller, chief scientific officer and executive vice president of PARI Pharma.

PARI Pharma's Phase IIb trial is a multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study to investigate the safety and efficacy of L-CsA in doses of 10 and 20 mg/day to prevent bronchiolitis obliterans in recipients of lung transplants. "We are seeing early success from our L-CsA program. This underscores PARI Pharma's unique position to combine formulation expertise with our advanced aerosol delivery technology to develop best in class therapies for unmet medical needs," added Martin Knoch, president of PARI Pharma.

Positive data regarding human lung deposition and distribution of L-CsA was published in the *Journal of Aerosol Medicine and Pulmonary Drug Delivery* last year, and clinical as well as preclinical data will be presented in April at the Annual Meeting of the International Society of Heart and Lung Transplantation in Chicago.

PARI Pharma focuses on the development of aerosol delivery devices and comprehensive inhalation drug development to advance aerosol therapies where drug and device can be optimized together. Based on PARI's 100-year history working with aerosols, PARI Pharma develops treatments for pulmonary and nasal administration customized with advanced delivery platforms, such as eFlow (lower respiratory) and Vibrent (upper respiratory) technologies. PARI Pharma partners with pharmaceutical companies to develop new or improved therapies. PARI Pharma has several clinical development programs ongoing, either partnered or on its own, for cystic fibrosis, asthma, COPD, respiratory syncytial virus infection, and treatments for lung transplant patients, among other indications. More information is available at www.paripharma.com.

Alexza and Biovail Form Collaboration to Develop and Commercialize AZ-004 (Staccato® Loxapine) in North America

PRNewswire: February 10, 2010 – MOUNTAIN VIEW, CA – Alexza Pharmaceuticals, Inc. (Nasdaq: ALXA) has established a collaboration with Biovail Laboratories International SRL, a subsidiary of Biovail Corporation (NYSE: BVF), to develop and commercialize AZ-004 (Staccato® loxapine) in the United States and Canada. AZ-004 is Alexza's lead program, based on the company's proprietary technology the Staccato system. Alexza submitted its New Drug Application (NDA) for Staccato loxapine in December 2009. Alexza is seeking regulatory approval to market AZ-004, an inhalation product candidate developed for the rapid treatment of agitation in patients with schizophrenia or bipolar disorder.

"We are very excited to be partnering our lead program with Biovail. Their key strategic focus and their CNS commercial plans match our view of an ideal partner for AZ-004," said Thomas B. King, Alexza president and CEO. "We believe that AZ-004, if approved, has the potential to change the treatment practices for acute agitation, as the only product able to meet both the patients' desire for quickly and comfortably gaining control of their agitation, and the clinicians' goal of rapidly and reliably calming an agitated patient."

"This agreement provides Biovail with a promising late-stage specialty CNS product," said Bill Wells, CEO of Biovail. "In clinical studies conducted by Alexza, Staccato loxapine rapidly delivered drug into the blood stream through the deep lung in a unique, non-invasive manner. We are delighted to be partnering with Alexza to bring this important treatment to market."

The collaboration provides for the development and commercialization of AZ-004 for multiple indications, including the proposed initial indication of treating agitation in schizophrenia and bipolar patients, as well as potential future clinical development in additional psychiatric and neurological indications and the symptoms associated with these indications. Biovail will lead the commercialization activities for AZ-004. Alexza will continue to manage the ongoing AZ-004 NDA review and approval process in connection with the initial indication and has entered into a manufacturing and supply agreement to supply Biovail clinical and commercial product.

Strativa Pharmaceuticals Provides an Update on Zuplenz® (Ondansetron) Oral Soluble Film

PRNewswire: February 5, 2010 – WOODCLIFF LAKE, NJ – Strativa Pharmaceuticals has announced that the U.S. FDA has issued a complete response letter regarding the New Drug Application (NDA) for Zuplenz® (ondansetron) oral soluble film for the prevention of nausea and vomiting associated with highly and moderately emetogenic chemotherapy, radiotherapy, and surgery.

Due to an agency-wide restriction on foreign travel in India, the FDA has been unable to perform an inspection of the clinical and analytical sites for a bioequivalence study and, therefore, cannot approve the application at this time. The FDA advised that they will schedule and perform an inspection of these sites as soon as possible. Strativa will continue to work with the FDA on completing these site inspections and finalization of product labeling. No issues related to the study data or film product were identified.

Strativa Pharmaceuticals, the proprietary products division of a wholly owned subsidiary of Par Pharmaceutical Companies, Inc. (NYSE: PRX), excels at finding, enhancing, and bringing to market drugs that make a meaningful difference to patients. For more information about Strativa, visit www.strativapharma.com.

Par Pharmaceutical Companies, Inc. is a United States-based specialty pharmaceutical company. Through its wholly owned subsidiary's two operating divisions, Par Pharmaceutical and Strativa Pharmaceuticals, it develops, manufactures, and markets higher barriers to entry generic drugs and niche, innovative proprietary pharmaceuticals. For more information, visit www.parpharm.com.

Access Pharmaceuticals Initiates Program Applying Cobalamin Platform to siRNA Drug Delivery

PRNewswire: February 4, 2010 – DALLAS, TX – Access Pharmaceuticals, Inc. (OTCBB: ACCP) has initiated an internal pre-licensing program to confirm the utility of its proprietary Cobalamin (vitamin B_{12}) platform technology for targeted delivery of siRNA therapies. The program is considered important because, despite the widely publicized potential of RNA therapy, researchers up to now have been stymied in their efforts to design a pharmaceutical product that efficiently transports siRNA therapeutics into the cells they are designed to inhibit or kill.

Access has multiple programs ongoing around use of its Cobalamin technology to facilitate oral absorption of pharmaceuticals, including previously announced collaborations with potential pharma and biotech partners. To date, its successful Cobalamin product development program has focused on the oral delivery of insulin and human growth hormone, two peptides that currently can only be given by injection. Because these two molecules share some of the same physical characteristics as RNA's active components, Access believes its Cobalamin technology could effectively deliver RNA therapy in an oral tablet instead of by injection.

A more compelling feature of the Cobalamin technology may be its ability to overcome the cellular transport obstacles that have held back fuller development of RNA therapy. The large size and high negative charge of RNA molecules prevents their absorption by target cells. Using the "Trojan Horse" principle, the Cobalamin nanoparticle technology can encapsulate small fragments of RNA (siRNA) and utilize Cobalamin's vitamin B_{12} uptake mechanism to transport them into target cells, allowing release of the active drug to initiate the therapeutic effect. Cobalamin's vitamin B_{12} uptake mechanism offers the potential for targeted delivery of siRNA because most human cells have a requirement for vitamin B_{12}. This is served by cell surface receptors, which facilitate absorption of this vitamin. In many diseases, the demand for vitamin B_{12} is increased, with a corresponding up-regulation of the receptor.

"Access scientists and collaborators have so far demonstrated in preclinical models that Cobalamin formulations are effective in achieving good oral drug delivery of charged peptides such as insulin and human growth hormone," commented David P. Nowotnik, senior vice president, research and development. "These successes with molecules which share some of the same physical characteristics as siRNA would indicate that we should now be able to generate effective formulations of Cobalamin nanoparticles for delivery of siRNA. We know already from previous work that we can make cancer drugs more effective using the Cobalamin approach, and so we have a sound scientific basis for the future development of Cobalamin RNAi therapeutics."

Cobalamin is Access' proprietary technology based on the use of vitamin B_{12} for targeted delivery of drugs to disease sites and for oral drug delivery of drugs that otherwise have poor oral bioavailability. Access has focused its Cobalamin product development program on the oral delivery of insulin and human growth hormone, two peptides that currently can only be given by injection. Since presenting promising results at a major conference in 2008, Access has made substantial improvements to the formulation technology. A new Cobalamin-coated insulin-containing nanoparticle formulation delivered orally provided a pharmacological response (lowering of blood glucose levels in an animal model of diabetes) equivalent to >80% of that achieved by insulin delivered subcutaneously. This represents a substantial oral bioavailability, indicating that this formulation has potential for clinical development and ultimate commercialization. Adaptation of this technology has provided a Cobalamin human growth hormone formulation that has demonstrated good efficacy, represented by >25% improvement in weight gain, when given orally in an established animal model. Access continues to move both products toward clinical development and plans to submit an additional patent application to protect the improvements to the technology.

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Launch of Ipsen's Decapeptyl® 6-Month Formulation (LP 22.5 mg) in France for the Treatment of Locally Advanced or Metastatic Hormone-Dependent Prostate Cancer

PRNewswire: February 4, 2010 – PARIS, FRANCE, and LAUSANNE, SWITZERLAND – Ipsen (Euronext: FR0010259150; IPN), an innovation-driven global specialty pharmaceutical group, and Debiopharm Group (Debiopharm), a Swiss-based global biopharmaceutical group of companies with a focus on the development of prescription drugs that target unmet medical needs, have announced the launch by Ipsen in France of Decapeptyl® LP 22.5-mg 6-month sustained release formulation for the treatment of locally advanced or metastatic hormone-dependent prostate cancer. Other launches are planned shortly, notably in Germany and Portugal.

The marketing authorization (MA) for this 6-month sustained release formulation of Decapeptyl® (triptorelin embonate 22.5 mg) was granted on November 10, 2009, by the French regulatory authorities (Agence Francaise de Securite Sanitaire des Produits de Sante [AFSSAPS]) for the treatment of locally advanced and metastatic hormone-dependent prostate cancer. France was the first country to approve Decapeptyl® LP 22.5 mg in the context of a decentralized procedure in Europe. The reimbursement rate by Social Security and the price setting decision have been published in the *Journal Officiel* of February 3, 2010, i.e., less than three months after MA was granted.

Decapeptyl® LP 22.5 mg is the new sustained release 6-month formulation of a gonatropin- releasing hormone (GnRH) agonist analogue developed by Debiopharm Group. Debiopharm has licensed the marketing rights to Ipsen for all territories where Ipsen currently commercializes triptorelin.

On October 13, 2009, Ipsen and Debiopharm Group announced the successful completion of the European decentralized registration procedure involving nine countries: Germany (reference member state), France, Austria, Finland, Norway, Belgium, Denmark, Spain, and The Netherlands, while for other European countries (Portugal, United Kingdom, Ireland, Italy, Romania, and Lithuania) the MA applications were filed as national line extensions to the existing Decapeptyl® applications.

Hovione's TwinCaps® Dry-Powder Inhaler Filed in Japan for the Treatment of Influenza

PRNewswire: February 2, 2010 – LOURES, PORTUGAL – Hovione has announced the filing of a new drug application in Japan by its licensee Daiichi Sankyo Company Ltd. for the influenza drug CS-8958, which is delivered using Hovione's TwinCaps® inhaler.

TwinCaps® is a pre-filled, disposable, and low-cost inhaler specifically developed for influenza indications and, thus, may be used for inhaled drug delivery to the lung in other acute indications, such as bacterial or viral infections. Since the inhaler was designed for a primarily inhaler-naive population, ease of use was the most important design criterion. Patents for TwinCaps® were filed worldwide in 2006 and have already been issued in Japan, South Africa, and Portugal. Hovione expects the case to proceed to the granting of patents in all jurisdictions.

CS-8958 is a laninamivir prodrug, a long-acting neuraminidase inhibitor developed as an inhaled drug by Daiichi Sankyo for the Japanese market. Clinical studies performed with adults and children suffering from type A or B influenza viruses have proven that the delivery of CS-8958 by TwinCaps® is effective with a single treatment course. Daiichi Sankyo has also announced the start of a Phase III clinical trial to demonstrate efficacy in influenza prevention.

Hovione has licensed its inhalation device patents to Daiichi Sankyo and Biota Holdings Ltd. (Victoria, Australia) and collaborated on the formulation development. Peter Villax, vice president in charge of TwinCaps® development, said "This filing follows four years of great collaboration between Daiichi Sankyo and Hovione and we are very honoured to be part of this project."

Hovione is a leading developer of inhaled drug products, with experience in anti-virals and proteins delivered by inhalation, as well as inhaler development. It is an international company with 50 years of experience in active pharmaceutical ingredient integrated development and compliant manufacture, from molecule to unit dose. In the inhalation area, Hovione is the only independent company offering such a broad range of services. For more information about Hovione, visit www.hovione.com or contact Corporate Communications, Isabel Pina at +351-21-982-9362 (telephone) or ipina@hovione.com (e-mail).

Anesthetic Approach Stops Pain without Affecting Motor Function

PRNewswire: February 18, 2010 – BOSTON, MA – One of the holy grails of local anesthesia is the ability to achieve a long-lasting nerve block that eliminates pain sensation while not affecting motor function. Researchers at Children's Hospital Boston have discovered an anesthetic approach that seems to do just that. If it proves to work in humans as well as it did in rats, it could be useful in a variety of medical applications, providing, for example, a local anesthetic for childbirth that would block pain without interfering with the mother's ability to push, or for musculoskeletal disorders in which it is important to maintain mobility. The discovery was reported by I. Sagie and D. Kohane in "Prolonged Sensory-Selective Nerve Blockade," in the online the *Proceedings of the National Academy of Sciences Early Edition* during the week of February 1.

The researchers, led by Daniel Kohane, MD, Ph.D., of the Division of Critical Care Medicine at Children's, originally sought only to find an agent that would prolong an anesthetic's effects. They focused on surfactants, a subclass of "chemical permeability enhancers" that enables drugs to spread more easily throughout a tissue. In testing three kinds of surfactant in combination with the anesthetics QX-314 and QX-222 (both derivatives of lidocaine), they found that this approach prolonged the sensory block in rats' sciatic nerves for up to 7 hours or more depending on the surfactant, but didn't prolong motor impairment; in some

cases the motor block was absent or of very short duration. In the rats, this meant they were able to tolerate having their paws on a hot plate for long periods, yet still able to balance and bear weight on their legs.

"This was a surprise finding," said Kohane, who also directs the Laboratory for Biomaterials and Drug Delivery at Children's. "What we've discovered really is a new approach; the question now is to figure out the mechanism by which it works and look at the effects of other chemical permeability enhancers." Kohane speculated that surfactant made the anesthetic better able to penetrate sensory nerves, which have little or none of the fatty coating known as myelin, whereas in motor neurons, which have abundant myelin, the active drug gets trapped in the myelin, never entering the nerve itself.

The lab's next steps will be to explore the effects of different permeability enhancers and examine their safety, since at high doses the drug combination could potentially be toxic to the nerves. The plan is to eventually test the approach in larger animals.

A parallel approach to achieving a pain-specific nerve block was proposed in 2007 by Clifford Woolf, MD, Ph.D., recently appointed director of the Children's Hospital Boston Program in Neurobiology. Woolf's team combined QXT-314 with capsaicin, which opens cellular gates that are only present in sensory neurons, and achieved pain-specific blocks in rats lasting 2 hours or more.

The new study was funded by the National Institutes of General Medical Sciences.

January 2010

Fuisz Pharma Announces Novel Anti-abuse System for Opiates

PRNewswire: January 27, 2010 – MIAMI, FL, and LJUBLJANA, SLOVENIA – Fuisz Pharma has announced the development of a novel anti-abuse system intended for use with abuse-prone drugs. This system seeks to address the misuse of addictive drugs, with a particular emphasis on opiates, and is applicable to all dosage forms.

Fuisz Pharma President Joseph Matus Fuisz commented, "The desirability of an effective anti-abuse system is well understood. The United States Government has estimated that thirty-six million Americans will abuse a medication at some point in their lifetime. Abuse is particularly prevalent in the pain area. Notwithstanding this need, the industry has found it challenging to implement abuse resistant dosage forms despite Herculean formulation efforts. This is due primarily to the fundamental tension between the bioavailability of a drug in the body and the prevention of extraction from the dosage form and other types of misuse by a highly motivated and sophisticated population of abusers." Fuisz continued, "The Fuisz system for preventing abuse combines, as the best inventions do, novelty with simplicity. We are confident that our anti-abuse system will be welcomed by our pharmaceutical partners as well as by those concerned with drug misuse issues and the public and private health practitioner."

Fuisz Pharma is a private pharmaceutical company originated by the Fuiszes. The Fuiszes have made substantial contributions in drug delivery in the areas of orally dissolving tablets and novel particle coating systems at Fuisz Technologies and inventing and developing thin-film drug delivery technologies at Kosmos Pharma and MonoSol Rx, etc.. They have extensive experience working with big and specialty pharma. Fuisz Pharma has offices in Miami and Los Angeles, as well as a presence in the European Union through Ljubljana, Slovenia.

LTS Teams Up with IntelGenx on VersaFilm

In-PharmaTechnologist.com: January 26, 2010 – Lohmann Therapie-Systeme (LTS) has signed up as a manufacturer of drugs that use IntelGenx's VersaFilm delivery technology. The deal will see Germany's LTS act as the exclusive manufacturer for pharmaceutical products that employ the polymeric film technology, three of which are currently being developed.

IntelGenx CEO Horst Zerbe explained that LTS is one of a handful of companies with the technical know-how and expertise required to undertake the large-scale, current good manufacturing practice standard production of this sort. Zerbe added that the accord "weds our pharmaceutical film development expertise with LTS's impressive manufacturing capabilities and scope, giving us the necessary tools to successfully develop novel film products from the bench through to regulatory approval." He went on to say that the most advanced of the VersaFilm-based drugs, a candidate migraine therapy, has completed pilot bioequivalency studies and that IntelGenx's plan "is to have LTS begin manufacturing scale up soon."

VersaFilm, as the name suggests, is a film-wafer technology developed to deliver drugs through the lining of the mouth which, according to IntelGenx, makes it particularly suited to conditions requiring a more rapid onset of action than can be provided by traditional pharmaceutical tablets. Headquartered in Quebec, Canada, IntelGenx is currently seeking commercialization partners for the technology and believes that VersaFilm application in lifecycle management may help it win just such a partner. The firm is already working with Azur Pharma, Dava Pharmaceuticals, Cary Pharmaceuticals, and Cannasat Therapeutics and is in discussion with several other parties that are interested in the VersaFilm technology in the pharmaceutical, food, and cosmetics industries.

Crospon Announces Spin Out of Janisys

January 25, 2010 – GALWAY, IRELAND – Crospon, a medical device developer based in Galway, Ireland, has announced that its drug delivery technology platform has been spun out into a distinct company, Janisys, as a result of the continued development of the product prototype.

The Janisys drug delivery platform, which leverages inkjet printing technology licensed from Hewlett-Packard, enables

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painless, controlled release of one or more drugs in a single patch to the skin. The announcement states that the new spin out is at a late stage in developing functional prototypes of its active microneedle-based transdermal system and the intent is to begin pre-clinical trials in 2010.

Janisys has secured co-development funding from a leading pharmaceutical company to progress the initial prototype development of Janisys, and the company will be seeking to engage in a round of fundraising during the first half of 2010 for completion of the commercial version of the system. The spin out of Janisys follows U.S. FDA approval of Crospon's flagship gastroenterology product, EndoFLIP®.

The Janisys skin patch delivers medication intradermally—just below the surface of the skin—thereby expanding the range of drugs and biopharmaceuticals for which patches may be used. The patch uses microneedles that barely penetrate the skin, which radically reduces discomfort compared to traditional hypodermic needles. The device will enable precise control of dosage timing, access to dosage history, patient activation mechanisms, and include inherent safety protocols for preventing adverse drug interactions.

Patent Granted to Chrono Therapeutics Inc.

PRWEB: January 16, 2010 – BASEL, SWITZERLAND, and HAMILTON, NJ – Chrono Therapeutics Inc. (CTI), a pioneer in chronotherapeutic healthcare products, has received notification from the European Patent Office that an additional and key patent for its ChronoDose™ technology has been granted. ChronoDose™ is a programmable passive transdermal drug delivery system that is tailored and optimized for patients and their individualized therapeutic needs and can be utilized for a broad range of compounds and therapeutic indications.

Guy DiPierro, CEO of CTI, stated, "This new patent grant affirms the novelty of CTI's technology, and we believe it will considerably reduce any potential risk to the CTI group." DiPierro also noted that this patent further strengthens CTI's intellectual property portfolio and that it, together with its other granted patents, should provide CTI with the protection needed for its global launch and strategic partnerships with the large, traditional industry leaders.

Chrono Therapeutics Inc. is evolving to become a global leader in chronotherapeutic-based healthcare drug products and is developing drug products in both the prescription and OTC markets. The significant advantages of chronotherapeutic-based therapies have now become widely recognized, and these applications are quickly coming to the forefront as the next major advance in treating many indications. CTI has previously completed significant clinical trials (2007), in which the ChronoDose™ system convincingly demonstrated multiple-dose functionality in human test subjects by accurately and reliably starting and stopping drug delivery, thereby achieving targeted plasma concentrations at programmed delivery intervals. For more information, contact Guy DiPierro, at +1.609.838.2572 or visit ChronoDose.com. ■

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Calendar of Events

2010

AAPS National Biotechnology Conference

May 16-19
Hilton San Francisco Union Square
San Francisco, CA, U.S.A.
www.aapspharmaceutica.com/nationalbiotech

7th Annual World Congress for Brain, Spinal Cord Mapping and Image Guided Therapy

May 24-27
Uniformed Services University of Health Sciences
Bethesda, MD, U.S.A.
www.ibmisps.org/

Chemistry, Manufacturing & Control (CMC): Quality, Regulatory and Scientific Requirements and Strategies

June 21-22
Shanghai, China
www.cpa.org.cn

37th Annual Meeting & Expostion of the Controlled Release Society

July 10-14
Oregon Convention Center
Portland, Oregon, U.S.A.
www.controlledreleasesociety.org/main/meetings

31EPS Satellite Symposium on Cell Penetrating Peptides

September 10-11
Panum Institute
Copenhagen, Denmark
http://icmm.ku.dk/forskerskole_i_genmedicin/genetic_medicine/symposium

Workshop Sponsored by CRS: Recent Advances in Controlled Release and Non-Invasive Drug Delivery of Biopharmaceuticals

September 20-21
Sheridan Baltimore Inner Harbor
Baltimore, MD, U.S.A.
www.aapspharmaceutica.com/meetings/workshops/NIDD

CRS Satellite Workshop: Novel Methods for Developing Clinically Relevant Product Specifications

November 13
Morial Convention Center
New Orleans, LO, U.S.A.
www.controlledreleasesociety.org/main/meetings

FIP Pharmaceutical Sciences 2010 World Congress (in association with the AAPS Annual Meeting and Exposition)

November 14-18
New Orleans, Louisiana, U.S.A.
www.pswc2010.org/

2011

38th Annual Meeting & Exposition of the Controlled Release Society

July 30-August 3
Gaylord National Resort and Convention Center
National Harbor, Maryland, U.S.A.
www.controlledreleasesociety.org/main/meetings