CRS Delivering Bioactives

Newsletter

A publication of the Controlled Release Society

Volume 26 • Number 3 • 2009

What's Inside

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

www.DrugDeliveryTech.com

For more information on print and online advertising opportunities call

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

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

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

CRS Newsletter
Delivering Bioactives

Vol. 26 • No. 3 • 2009

Table of Contents

Advertisers' Index

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.

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

Telephone: +1.651.454.7250
Facsimile: +1.651.454.0766

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

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

From the Editor

Yvonne Perrie
Aston University, School of Life and Health Sciences,
Aston Triangle, Birmingham, U.K.

Within this issue we have a true feast of interesting articles, reviews, and interviews, and we can see 2009 is shaping up to be a jam-packed year for CRS. This year also marks the anniversary of some major scientific achievements: it is 200 years since Charles Darwin's birth and 150 year since the publication of *On the Origin of Species*. It has also been 20 years since Tim Berners-Lee circulated a proposal "HyperText and CERN" around CERN for comments. This proposal was further refined by Tim Berners-Lee and Robert Cailliau in 1990 and eventually became the World Wide Web. For most of our day-to-day activities, the outcome of Tim's proposal has had a great impact. For example, whilst we bemoan students for "googling" everything, many of us are fellow culprits. Yet in defence of us all, what the Internet offers is a dangerous cocktail of more information than we can ever read, need, or use combined with a plethora of communication portals. But, it can also be nicely exploited for pedagogic means, check out page 22 for a good set of fun teaching tools.

Then there is e-mail. Apparently 59% of us with portable devices check our e-mail every time one pings into our mailbox. Based on this, it is understandable that we get grumpy when the wireless is slow, and we find ourselves constantly trawling around looking for power sockets to feed our power hungry e-systems. If you were wondering if U R addicted to e-mail, some worrying symptoms can include (1):

1. You wake up at 3 a.m. to go to the bathroom and stop to check your e-mail on the way back to bed.
2. You sleep with your iPhone (or Blackberry, if you're still a little old school!) under your pillow.
3. You can type 70 words per minute but can't read your own handwriting.
4. You don't know the gender of three of your closest friends, because they have neutral nicknames, and you have never actually met them.
5. You refuse to go on holiday if there is no reception for your phone.
6. You e-mail your son/daughter in their room to say dinner is ready. They e-mail back "What's for dinner?" You then direct them to the family Facebook site.

There are so many ways to communicate these days—blogs, wikis, forums, and twittering, to list a few. Many of these give us a degree of anonymity and informality and such environments have led to what is referred to as "flaming"—which is basically an act of outrageous rudeness between Internet users via e-mail or in forums (see *Wikipedia* for further details—☺, LOL, and all that). Its etymology is linked to a superhero of the name Johnny Torch, who bursts into flames when upset (2). Yet, anonymity in the scientific field is not new; peer-review is long established in our community, and whilst not as blunt as the flaming often used on Internet fora, reviewers have been known to get some snidey utterances past the editors (2).

What is written	**What is meant**
I read with interest…	*You're a fool, and I lost interest extremely quickly*
With all due respect…	*No respect is meant at all*
It is clear from these results…	*There is nothing clear from this at all, but perhaps you will not notice if I say it with a touch of arrogance*
Something positive followed by 'but' then a string of negatives	*Just a way of building false hope*

From the Editor continued on page 4

Lisbeth Illum
IDentity, Nottingham, U.K.

It is hard to believe, but this is the last issue of the *CRS Newsletter* in my presidential year and, hence, the last "From the President" that will be from my hand. I hope you have read these notes with an open mind and in the spirit in which they were given. I thought it would be appropriate (although the members of the CRS are the ones to do the judging) to look at what I, as the new president, promised to do when I gave my inaugural speech in New York last summer and what has actually been achieved during this time.

CRS Goals for 2008–2009

CRS Needs to Be Run on a Strong Business-like Footing
The BOD over the last year has completed and updated the five-year strategic plan that was started the year before under the leadership of CRS President Susan Cady. The plan contains the mission and vision of the CRS and the goals the BOD will strive to achieve over the next five years with the help of the whole Society. Without a strategic plan, the CRS cannot move forward in a structured and functional way. The BOD has also started preparation of a business plan for CRS based on income streams from present and new CRS activities. The business plan is expected to be ready for presentation at the CRS Annual Meeting this summer.

CRS Needs to Be Less Dependent Economically on the Annual Meeting
CRS has over the past year increased the number of scientific satellite meetings and educational workshops, not only for the benefit of our members but also to create additional income for the Society. The BOD is also planning to hold a second smaller meeting yearly that is specifically focused on one or two scientific areas, in addition to the current annual meeting. We have also initiated the CRS publication program, starting with four book titles edited by distinguished scientists and world leaders in their fields to be published within the next two years. Furthermore, we have created an exciting opportunity for the publication of the first new CRS journal since JCR.

CRS Needs to Be on the Cutting Edge of New Science
I hope you will all agree that due to the never-ending hard work of Scientific Secretary Ijeoma Uchegbu the scientific programs for the CRS Annual Meeting in New York were outstanding. The attraction of new outstanding speakers to the workshops and sessions created a breath of fresh air. The CRS Annual Meeting & Exposition in Copenhagen is set to present the newest and most exciting science in the delivery of bioactives and other functional materials, with the involvement of pharmaceutical and other companies and universities from around the world. Furthermore, we have also in our own workshops and in co-sponsored events reached out to new exciting areas of research, such as "RNA Interference Biology and Therapeutics" at the annual meeting in Copenhagen.

CRS Needs to Increase the Number of CRS Chapters to Be a Truly Global Society
The BOD (especially Mark Tracy) and the China Initiative Subcommittee have been working hard over the past year to produce a plan for the increased interaction of Chinese scientists with the CRS and to set up a workshop in China. CRS has already been a co-sponsor with AAPS of the first workshop in China, namely the Asian Arden House meeting on Particles and Powder Technologies for Solid Dosage Forms, in Beijing, in October 2008. CRS will also be a sponsor of the International Pharmaceutical Conference in Shanghai in September 2009. The BOD feels that the CRS needs to build relations with Chinese scientists, which may be followed by the establishment of a Chinese chapter. Hopefully, other countries such as Japan, Russia, and South Africa will follow.

CRS Needs to Increase Its Value to and Its Communications with Its Members
We have over the last year improved the CRS website, which is normally the first point of interaction with members. The website is now much more interesting and interactive, and much more information (scientific and otherwise) is now available at the touch of a finger. We have also managed to launch webinars on the website, albeit only two so far. So far not a great achievement, but I promise you more will come. The mentor/protégé program that was started last year has grown successfully over this year as well. In addition, a questionnaire has been sent out by CRS to all members and past members to help CRS find out what we are doing right and wrong and what members and members to be would like to be offered by CRS. The results have just come in, and a report will soon be available on the CRS website. Finally, I would like to mention the work of the Young Scientist Committee under the leadership of Farid A. Dorkoosh and Dody L. Reimer, who have done a fantastic job in making the scientific and other activities for young scientists offered at the CRS Annual Meeting and throughout the year truly outstanding.

CRS Needs to Increase the Number of Members
In the last year we initiated a new and active Marketing Committee (under the leadership of Claire Madden-Smith). The committee has worked hard to find ways in which to make CRS more attractive to a wider range of scientists. So far the member number has increased a bit, but not enough. We are currently looking at new ways to provide incentives for existing members to spread the word about CRS and recruit new members among their colleagues.

From the President continued on page 4

From the Editor continued from page 2

Such veiled comments between scientists may even span centuries. Isaac Newton's famous note to Robert Hooke "If I have seen a little further it is by standing on the shoulders of giants" is allegedly a sarcastic comment against the vertically challenged Hooke (2). However, given Newton's other memorable comment, "Tact is the knack of making a point without making an enemy," this could just be people reading too much between the lines.

TTFN and c u soon in Copenhagen!

Yvonne Perrie

References

1. www.jardmail.co.uk/misc/netaddict.shtml
2. Fong, K. With no due respect, LOL, Times Higher Education, January 8, 2009. ■

From the President continued from page 3

All in all, I think much has been achieved by the BOD over the last year, due in large part to the never-ending and highly appreciated help provided by the many committees filled with enthusiastic volunteers.

I shall finally urge you to participate in the CRS Annual Meeting & Exposition in Copenhagen in July. The program of the meeting is absolutely bursting with exciting and novel topics and world-renowned speakers. For small and mid-sized pharmaceutical companies, the meeting provides a fantastic opportunity to distribute the message of your company's products and many opportunities for collaboration, especially during scientific and soapbox sessions. Likewise, there is an outstanding opportunity for CROs and CMOs to participate as exhibitors and to meet many potential customers.

It would be really good to hear from you all whether you have any comments on the work that has been going on over the past year and on the activities of CRS or suggestions for other activities that in your view would be important for the future of CRS. After all, this is your Society. Please contact me at my e-mail address (lisbeth.illum@illumdavis.com).

Lisbeth Illum ■

CRS Headquarters & Staff

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

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

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

Barbara Mock, *Vice President of Finance*
+1.651.994.3829 • bmock@scisoc.org

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

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

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

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

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

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

Ronda Thompson, *Program Supervisor & Sponsorship Sales*
+1.651.994.3836 • rthompson@scisoc.org

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

CRS
Delivering Bioactives

Interview with Dr. Jorge Heller[1]

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

Note

It is with great sadness that I learned of Dr. Jorge Heller's passing on June 8, 2009. My graduate student (Brian Kilfoyle and co-author) and I had been in touch with Dr. Heller over the past weeks while preparing this interview article. Neither of us realized how ill he was. After finishing the article, we had requested that he send us a photograph of himself with higher resolution for publication. This prompted his response, which we received on June 2, saying that he would try to look for one but that he felt ill at the time. This would be his last message to us. We feel so lucky right now that we were given the opportunity to complete this interview. Dr. Heller was an extremely sweet person with a lifetime of accomplishments, and he will be missed by us all.

Dr. Jorge Heller

Introduction

Dr. Jorge Heller has had a long and prestigious career in polymer chemistry. He has been a leader in the field for many decades and continues, in retirement, to work in the field of controlled drug delivery.

Dr. Heller received his B.S. degree in chemistry from the University of California at Berkeley and his Ph.D. degree in organic chemistry from the University of Washington in Seattle. Upon graduation, he worked for Union Carbide in a position that introduced him for the first time to polymer chemistry. This program impacted the rest of his career and made him more of a polymer chemist than an organic chemist. After three years in this position, Dr. Heller decided to bring his newly learned skills back to academia and accepted a position with Stanford University as part of the Stanford Research Institute in Menlo Park, CA. At the institute, Dr. Heller was placed in charge of the newly formed polymer program. This position allowed him additional freedom to explore subjects of interest to him. Dr. Heller spent many years at the Stanford Research Institute and became the director of the Controlled Release and Biomedical Polymers Department. In the late 1960s, he received a call from Alex Zaffaroni and joined ALZA as director of physical sciences.

At ALZA, he was charged with developing a bioerodible drug delivery system, his first foray into controlled drug delivery. This task was achieved by the development of poly(ortho esters). In 1974, Dr. Heller left ALZA and rejoined the Stanford Research Institute, where he continued working with poly(ortho esters). In 1994, he left Stanford to join AP Pharma, as a principal scientist.

[1] Please see the obituary published on page 8 in this issue of the *CRS Newsletter* for more information on the life and career of this pioneering scientist.

Dr. Heller has held adjunct appointments at many universities, is the founder of the *Journal of Controlled Release*, and is a past president of the Controlled Release Society (1989–1990). Throughout his career, Dr. Heller's contributions have been recognized with many awards, including the CRS Distinguished Service Award, the CRS Founders Award, the Clemson Award for applied biomaterials research (1980), AAPS Fellowship (1993), Society for Biomaterials Fellowship (1994), and the SRI Fellowship, with paid sabbaticals at the University of Keele with Ruth Duncan, University of Geneva with Robert Gurny, and University of Utah with Sung Wan Kim. Dr. Heller was honored at the 7th International Symposium on Recent Advances in Drug Delivery Research (1995).

Dr. Heller recently retired but remains very much involved. He runs a consulting business, Heller Consulting, and recently co-founded Branching Tree, a company based in the Netherlands that is working with thermogel systems.

Interview

Q ***When you graduated from the University of Washington with your Ph.D., what factors played a role in your decision to go to Union Carbide as opposed to other companies and/or university positions?***

A At that time in the early 1950s, I believed that industry would best fit my needs. I selected Union Carbide because they offered me a full-time technician, significant resources, and an almost total freedom to try and unravel the complexities of the Ziegler-Natta catalysis, at that time a hot topic.

Q ***You've worked in both academia and industry throughout your career. What are the key pros and cons for each?***

A The major attraction of an academic career is the total freedom to choose research and subjects areas. This clearly is not the case with industry, where research is regulated and designed to produce products that will ultimately make money. For this reason, even though my career at Union Carbide was quite successful, I did not want to be controlled, so I decided to leave and join Stanford Research Institute, at that time a small, prestigious institution owned by Stanford University, where I could pursue subjects of my choosing.

Q ***What scientists have most impacted your career?***

A It is not easy to look back on a career that spans five decades and identify those that most influenced my career. But if I had to do that, I would mention Allan Michaels, who planted the seed of bioerodible polymers and surface erosion; Bob Langer, who invited me to teach at the yearly MIT course; the late

Interview with Dr. Jorge Heller continued on page 6

Interview with Dr. Jorge Heller continued from page 5

Joe Robinson, with whom I traveled the world and absorbed much of his knowledge and passion for research; Sung Wan Kim, who got me interested in bioerodible thermogels; and Nicholas Peppas, who has been a good friend for all these years.

Q ***What role has controlled release played in your research?***

A While at SRI, although I had no formal polymer training, I worked on various synthetic polymer projects, largely designed to produce polymers with improved thermal stability. This allowed me to acquire considerable expertise in synthetic polymer chemistry. I also began to teach a course in polymer science at the San Jose State University. Then, fate intervened. I received a call from Alex Zaffaroni, who invited me to join a new company he just formed, ALZA, as director of physical sciences. While this meant giving up a very successful career at SRI and joining what at that time was an unknown venture, the subject of controlled release so fascinated me that I resigned from SRI and joined ALZA. This was in early 1970, and I have worked full time on controlled drug release ever since—now 39 years. So clearly, controlled drug release has been an integral part of my research for many years.

Q ***What were the crucial steps in the discovery of the poly(ortho esters) and how have they impacted your career?***

A While at ALZA, Allan Michaels, a former MIT professor now deceased, who also joined ALZA, challenged me to develop an ALZA proprietary polymer that would undergo surface erosion and, thus, be able to release incorporated drugs by an erosion-controlled process rather than by a diffusion controlled process. After some thought, I decided that what we needed was a very hydrophobic polymer with labile linkages that would erode from the outside in. And, a search of suitable linkages showed that an ortho ester would be an excellent candidate. So, the first example of a poly(ortho ester) was developed at ALZA, but was never seriously pursued.

After four years at ALZA, I decided to return to SRI, which subsequently separated from Stanford University and became SRI International, where I remained for the next 30 years. I decided to continue work with poly(ortho esters) because I was totally convinced that they had a significant potential for becoming an important delivery system.

Photo by Dr. Jorge Heller.

However, I needed to develop a new synthesis outside the patents held by ALZA. Fortunately, ALZA left a gaping hole in their patent coverage and did not cover the preparation of poly(ortho esters) by the addition of diols to diketene acetals, and that is what I began exploring. After considerable difficulties, mainly related to the preparation of a suitable diketene acetal, which actually took two years to develop, this turned out to be a very successful synthesis, and over the years a number of different poly(ortho ester) families were developed.

In particular, the most recent poly(ortho ester) is under active development at AP Pharma and has completed a Phase III clinical trial for the treatment of chemotherapy-induced nausea and vomiting. This was a major milestone and demonstrated that poly(ortho esters) are safe and suitable for use in human therapeutics.

Other applications are also under development at AP Pharma, although due to the current economic situation, these have been discontinued. In 1990 I left SRI International and joined AP Pharma as principal scientist to help with the commercialization effort. I was already on their Board of Directors, so the move was a logical one. Clearly, poly(ortho esters) have had and continue to have a significant impact on my professional life.

Q ***You've mentioned in the past that in the 1950s polymer science was not taught and was even somewhat looked down upon. In your view, what key discoveries or events precipitated the transformation that has resulted in the key role that polymer science now plays?***

A I believe that in the early 1950s the culprit was mainly ignorance and that polymers were associated with the tarry residue left over from a distillation. Some people even referred to polymer chemists as gunk-chemists. But largely due to giants in the field such as Speed Marvel, Paul Flory, Humes Carothers, Herman Mark, and others, along with the fact that a great number of chemists went to industry to do polymer research, changed all that, and polymer science is now a respected and mature discipline.

Q ***Could you recommend a publication or two that would be particularly noteworthy for our CRS readers?***

A My work with poly(ortho esters) is summarized in two publications.

Poly(ortho esters), *Advances in Polymer Science* 10: 41-92 (1993).

Poly(ortho esters): Synthesis, characterization, properties and uses, *Advances in Drug Delivery Reviews* 54: 1015-1039 (2002).

In addition, we have also worked on self-regulated drug delivery systems and were the first to show that drug release can be modulated by the presence and concentration of an agent external to the device. That work is summarized in chapter 5 in *Pulsed and Self-Regulated Drug Delivery Systems*, Joseph Kost, ed., CRC Press (1990).

Q ***As a former president of the Controlled Release Society and the founder of the* Journal of Controlled Release*, what important role(s) do you think the Society has played since its inception?***

A First, a better name for the *Journal of Controlled Release* would be Journal of Controlled Delivery. At various times we considered a change in name, but that turned out to be so complicated that we abandoned such efforts.

The Controlled Release Society was founded by Nate Cardarelli in 1973 as a veterinary and agricultural controlled release organization. When human therapeutics lectures began to appear in the program, there was significant resentment by the veterinary component that felt that human therapeutics was beginning to dominate their meetings. However, this was eventually resolved, and now, even though there is a veterinary component, the major focus of the Society became human therapeutics. In 1985 the Society took its first steps to become an international society by holding its first international meeting run by Nicholas Peppas and Robert Gurny in Geneva, Switzerland, and I ran the second international meeting in Basel, Switzerland, during the Nicholas Peppas presidency. Now, the CRS meetings are a major annual event.

In the early days, our major preoccupation was developing better polymers and processing techniques, as well as achieving zero-order drug release. However, this has now drastically changed, and the field is rapidly becoming focused on biology and drug interactions with living organisms.

So, from a modest and not very sophisticated beginning, the Society has become a major factor in bringing together a diverse collection of scientists from many different disciplines.

Q ***What do you think the future holds for controlled drug delivery? What role will polymer science play in this?***

A Polymer science will always play an important role in controlled drug delivery, but the emphasis is changing from developing devices such as microspheres or strands to more sophisticated applications such as gene therapy and targeted devices. Especially important is nanotechnology, where microscopic devices can seek out and deliver their payload to destroy diseased tissue without patient intervention. The development of such devices will require sophisticated use of polymer science.

Another important use of polymer science is related to "patient friendliness," which means developing devices that can be administered using a small-bore needle that will cause minimal discomfort for the patient. One example of such a system are thermogels, and their development now occupies a significant portion of my time. In fact, I am participating in forming a company in the Netherlands, called Branching Tree, to commercialize a series of synthetic thermogels.

Q ***Can you tell us more about Branching Tree?***

A Branching Tree is a start-up company in the Netherlands founded by Mike de Leeuw, Etienne Schacht at the University of Gent, and myself. Mike de Leeuw is a biochemist who has significant experience in starting new companies. At this time, we have some in-house developments and are in the process of licensing a number of promising thermogel systems and demonstrating their usefulness. We are also developing collaborations with academic institutions.

A thermogel is a material that at room temperature is water-soluble and at body temperature forms a firm gel. This makes them almost ideally suited to deliver proteins, since the protein is simply dissolved in the same solution that contains the water-soluble thermogel and is injected. This forms a depot from which the protein is slowly released by erosion, diffusion, or a combination of the two mechanisms. What is particularly attractive is that the proteins are only exposed to water and a maximum temperature of 37°C, so that their activity should not be compromised. And, because they are administered using a very small-bore needle, a number of ocular applications are possible.

Q ***What personal attributes allowed you to be so successful throughout your career?***

A There are no shortcuts, and success can only come after hard work, a total dedication to one's chosen field, and a true love of science. It is also important to never give up. All problems have a solution, and with sufficient effort, they can be solved.

Photo by Dr. Jorge Heller.

Q ***In retirement, what hobbies have you picked up?***

A My wife and I selected Ashland as a place to retire, mainly because it is the home of the annual Shakespeare festival and also has significant activity in music, both symphonic and choral. There are additional theaters in the area plus many art galleries, so there is something to do almost every day.

I have always had a serious interest in photography and having converted to digital photography has been a major step forward. I live in a beautiful area of Oregon, and nature photography is for me an important activity.

Q ***How has your consulting business developed?***

A My consulting business began with a contract with AP Pharma to continue poly(ortho ester) development after I formally retired. After three years of consulting for AP Pharma, we parted company, and I have continued limited consulting for other companies.

Q ***What does it mean to you to have the CRS Outstanding Paper Award named in your honor?***

A I am truly honored that my contributions to the *Journal of Controlled Release* have been recognized by the CRS, and I enjoy presenting the award to the recipients. ■

In Memory of Jorge Heller

CRS sadly announces the passing of Jorge Heller on June 8, 2009.

Jorge Heller was born in Czechoslovakia in 1927 and moved with his family to Argentina in 1939. After completing high school in Buenos Aires, Jorge moved to the United States in 1948.

Jorge had a long and prestigious career in applications of polymer chemistry for controlled release. He was a leader in our field for many decades and continued in his retirement to work in controlled drug delivery. From the inception of CRS, he was a very active member of the Society and served as president from 1989 to 1990. He was also the founder and editor of the *Journal of Controlled Release*, and to this day, the *Journal of Controlled Release* Award is given in Jorge Heller's name.

Jorge received his B.S. degree in chemistry from the University of California at Berkeley and his Ph.D. degree in organic chemistry from the University of Washington in Seattle. In his position at Union Carbide, he was introduced for the first time to polymer chemistry. After three years, he accepted a position with Stanford University as part of the Stanford Research Institute (SRI) in Menlo Park, CA, and was put in charge of the newly formed polymer program. Dr. Heller spent many years at SRI and became the director of the Controlled Release and Biomedical Polymers Department. In the late 1960s, he joined ALZA as director of physical sciences and was charged with developing a bioerodible drug delivery system, his first foray into controlled drug delivery. This task was achieved by the development of poly(ortho esters). In 1974, Dr. Heller left ALZA and rejoined SRI, where he continued working with poly(ortho esters). In 1994, he left SRI to join AP Pharma as a principal scientist. For almost 30 years, Dr. Heller taught the Advances in Controlled Drug Delivery course at MIT, where he passed on his extensive knowledge to more than 4,000 researchers and engineers from industry.

Dr. Heller held adjunct appointments at many universities. His contributions have been recognized with many awards, including receiving the Society for Biomaterials' Clemson Award for applied biomaterials research (1980), being elected as a Fellow of the American Association of Pharmaceutical Scientists (1993) and of the Society for Biomaterials (1994), receiving the CRS Distinguished Service Award (1995), and, most recently, receiving the CRS Founders' Award (2006). Dr. Heller received the SRI Fellowship, with paid sabbaticals at the University of Keele with Ruth Duncan, University of Geneva with Robert Gurny, and University of Utah with Sung Wan Kim. The 7th International Symposium on Recent Advances in Drug Delivery Research was held in Dr. Heller's honor in 1995.

Taking chances was something Jorge Heller was known for, and his colleagues admired him for being a gambler. The big change that impacted his life was taking the position at ALZA, as the director of physical sciences. Controlled drug delivery was a new concept at the time, and Dr. Heller knew joining this new company was full of risks. His tenure at ALZA brought him into the world of controlled drug delivery and the development of poly(ortho esters). Jorge Heller became one of the most sought-after leaders in controlled release and delivery.

When Dr. Heller was recently asked, "What personal attributes allowed you to be so successful throughout your career?"

He replied, "There are no shortcuts, and success can only come after hard work, a total dedication to one's chosen field, and a true love of science. It is also important to never give up. All problems have a solution, and with sufficient effort, they can be solved."

Dr. Heller was an eminent scientist and will be remembered for his never-ending enthusiasm for research, new areas of science, and interest in the welfare and development of young scientists. Since the start of the CRS, he only missed one annual meeting and exposition due to illness and had just informed us that unfortunately due to his health he would not be able to join us in Copenhagen.

Dr. Heller is survived by his wife, Gloria Heller, as well as a son in California, a son in Washington, numerous grandchildren, a brother in Argentina, and many cousins, nephews, and nieces.

Dr. Nicholas Peppas, long-time friend and colleague of Jorge Heller, says,

> Jorge Heller was a great contributor to the fields of controlled drug delivery and polymer science. His pioneering work on biodegradable systems catalyzed our growth of this field. He was an international ambassador for drug delivery. His bold vision to start JCR in 1984 allowed the field of controlled release to mature and the Controlled Release Society to become truly international. By 1989, when he took over as CRS president, JCR had become the 'most desirable journal for publication of controlled release research,' while CRS had done two international meetings already (Geneva, Basel) and was on the way to international leadership. Without this visionary effort in the early 1980s, this would have been impossible.
>
> But more than anything else, Jorge Heller remained a simple man, always smiling, always supporting the young generation of scientists…. He loved flying all over the country (he was a great pilot), searching all music stores for the latest editions of old performances (Vladimir Horowitz and Jascha Heifetz were his favorites), and he would always enjoy a great scotch, before the doctors curtailed such activities.
>
> I am thinking that the late Joe Robinson (who was teaching the MIT course with him) would always tease him and call him 'the grandpa of the field.' I am sure that today Jorge and Joe, father and son, are having a nice scotch up there and enjoying the fruits of their great scientific leadership and their great contributions for the betterment of our patients' quality of life.

Jorge Heller will be missed. His contributions will keep him with us. Thank you, Jorge! ■

In Memory of Robert Sparks

Robert Edward Sparks, age 78, a professor, biomedical researcher, consultant, and inventor, died March 21, 2009, at his home in Kirkwood, MO, USA.

Bob was a long-time member of the Controlled Release Society and served on the Board of Scientific Advisors. He was also involved in re-energizing the Consumer and Diversified Products group within the organization, often lecturing in educational workshops prior to annual meetings.

Bob earned a B.S. degree from the University of Missouri and a Ph.D. degree in engineering from Johns Hopkins University, after which he joined the faculty of Case Western Reserve University. In 1972, Bob was named director of the Biological Transport Laboratory at Washington University in St. Louis. He left Washington University in 1994 to found Particle and Coating Technologies, a St. Louis-based contract research organization that focused on controlled release applications in the pharmaceutical and consumer products industries.

Bob was a past president of the American Society for Artificial Internal Organs. He spent a lot of his life teaching in academics, as well as with the Center for Professional Advancement and gave invited lectures around the world. He was greatly respected by his friends, colleagues, and former students as a true gentleman and scholar. ■

CRS Volunteer Opportunities for You!

Abstract Reviewer
Award Committees
Chapters
Consumer & Diversified Products Committee
Education Initiative Subcommittee
Educational Workshop/Satellite
Meeting Review Committee
Marketing Committee
Membership & Development Committee
Mentor/Protégé Subcommittee
Nanomedicines Group
Oral Drug Delivery Group
Planning & Finance Committee
Publishing Subcommittees
Session Chair
Tablet Manufacturing Group
Veterinary Committee
Webcast Subcommittee
Website Design Committee
Young Scientist Committee

Visit http://www.controlledreleasesociety.org/main/about/form_Volunteer.cfm for more details.

Star-like Antibody-Targeted Polymer-Drug Conjugates

Tomáš Etrych,[1,2] Lubomír Kovář,[3] Milada Šírová,[3] Blanka Říhová,[3] and Karel Ulbrich[1]

Summary
The synthesis, physico-chemical, and biological properties of star-like antibody-containing HPMA-based polymer conjugates tailored for site-specific delivery of drugs are described. In the synthesis of the antibody-containing conjugates, semitelechelic polymers are used for one-point attachment to modified anti-CD20 antibody (AtB), resulting in a star-like structure. The method of antibody modification, using 2-iminothiolane or dithiothreitol, strongly influenced the number of introduced reactive sulfhydril groups and binding efficacy of the conjugates to cells.

Introduction
Water-soluble synthetic polymers and their conjugates with antibodies or oligopeptides provide a potential targetable drug delivery system. In our recent papers we described the synthesis of targetable *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymers (1–3) containing the anticancer drug doxorubicin (Dox) bound to the polymer via pH-sensitive hydrazone linkage. We demonstrated that these conjugates exhibit high cytotoxicity for T cell lymphoma EL4 cells and a significant therapeutic effect in the treatment of EL4 lymphoma in mice (2–4). In this study we describe the synthesis and properties of anti-CD20 antibody-targeted polymer-drug conjugates designed for tumour therapy. In the synthesis of the conjugates, semitelechelic polymers are used for one-point attachment to the antibody, resulting in a star-like structure (Figure 1), with the aim of preserving the binding efficacy of AtB to appropriate receptors on the cells.

Experimental Methods
Synthesis of Polymer Precursors. Semitelechelic HPMA copolymers, polymer precursors containing hydrazide groups randomly distributed along the polymer chain, were prepared by the radical copolymerization initiated with a new azo-initiator, 4,4′-azobis(4-cyanovaleric acid thiazolidine-2-thione) (ABIK-TT). The copolymer chain-terminating reactive maleimide (MI) or pyridyldisulfanyl (PDS) groups were introduced to the copolymers by the reaction of the polymer thiazolidine-2-thione group with an amino group of *N*-(2-aminoethyl)maleimide or 2-(2-pyridyldisulfenyl)ethylamine. In both cases, the polymer conjugates with Dox bound to the copolymer with hydrazone linkages were prepared by the reaction of the hydrazide groups containing polymer precursors with Dox hydrochloride at room temperature in the dark.

Synthesis of Antibody-Targeted Polymer-Drug Conjugates. Two different star-like antibody-targeted polymer conjugates differing in their structure were synthesized (Table 1). The conjugates were prepared by the reaction of a thiol-containing antibody with the semitelechelic polymer precursors containing a chain-terminating MI or PDS group. In the first system, a thiol-containing antibody was prepared by the reaction of amino groups of antibody with 2-iminothiolane (ITH) (ITH-modified antibody). The second type of thiol-containing antibody was obtained by reduction of disulfide bridges in a structure of the antibody with dithiothreitol (DTT) (reduced antibody).

Results and Discussion
Synthesis of Semitelechelic Polymers. The method of preparation of semitelechelic polymer precursors was based on radical copolymerization of HPMA with a hydrazide derivative of methacrylic acid initiated with ABIK-TT, an initiator containing reactive TT groups. Use of this initiator enables synthesis of semitelechelic copolymers with reactive chain-terminating TT groups. The molecular weight and functionality of such semitelechelic polymers could be precisely controlled by concentration of an initiator and other reactants in a polymerization mixture. A chain-terminating TT group enables one-point attachment of a semitelechelic polymer, e.g., to the molecule of antibody or other biologically active protein, or simple transformation to another chain-terminating reactive group.

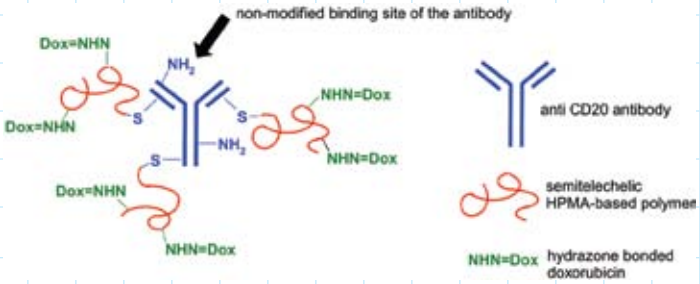


Figure 1. *Schematic structure of star-like antibody-polymer-Dox conjugate.*

Table 1. Physico-chemical characteristics of star-like polymer-drug conjugates

Polymer Conjugate	AtB (wt%)	Dox (wt%)	M_w (g/mol)	M_w/M_n
1[a]	28.3	5.7	683,000	2.10
2[b]	55.9	-	296,000	1.52
3[c]	41.2	-	346,300	1.56
4[c]	45.3	5.3	334,000	1.60

[a]AtB modified by ITH; semitelechelic polymer with MI group.
[b]AtB reduced by DTT; semitelechelic polymer with PDS group.
[c]AtB modified by DTT; semitelechelic polymer with MI group.

[1] Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, v.v.i., 162 06 Prague 6, Czech Republic.
[2] Corresponding author. Tel: +420-296809224; Fax: +420-296809410; E-mail: etrych@imc.cas.cz.
[3] Institute of Microbiology, Academy of Sciences of the Czech Republic, v.v.i., 142 20 Prague 4, Czech Republic.

Synthesis of Star-like Antibody-Targeted Polymer-Drug Conjugates. Modification of antibody with ITH led to the introduction of up to 35 sulfhydril groups per antibody, while reduction of AtB with DTT allowed the introduction of up to 12 sulfhydril groups per AtB. On the other hand, reduction with DTT did not significantly change the binding side of the antibody, whereas in the case of ITH modification damage to the AtB binding site can occur.

In the case of polymer containing the chain-terminating MI group, we observed a very rapid conjugation reaction with modified antibody. When a polymer containing a PDS group was used, conjugation with the antibody was slower, and the number of polymer chains attached to one antibody molecule was lower than in the previous case.

Release of Dox from the Conjugates. The results of *in vitro* Dox release measurements showed that the conjugates were quite stable in buffer solutions at pH 7.4 and 37°C, only a small release of Dox was observed within 24 hr of incubation. On the other hand, around 90% of Dox was released within 24 hr in a buffer at pH 5 and 37°C. The rate of Dox release in a buffer at pH 5 depends only slightly on the detailed structure of the antibody-polymer-Dox conjugates. We found that conjugation of semitelechelic polymer-Dox conjugate to the antibody resulted in a small decrease in the rate of Dox release in a buffer at pH 5 (4–7% of Dox after 24 hr).

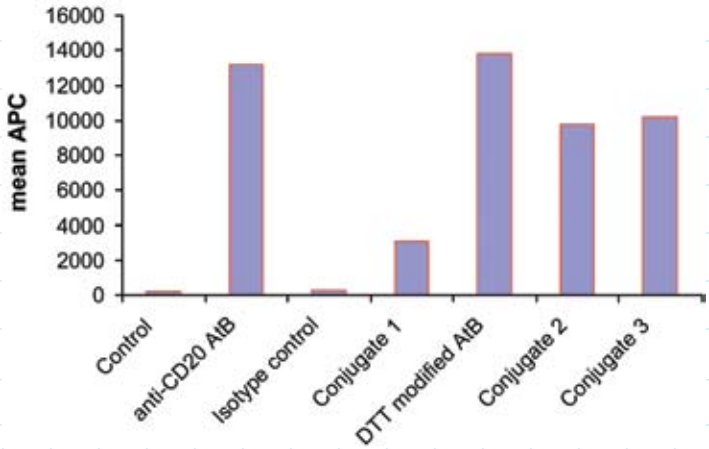


Figure 2. In vitro *binding assay of anti-CD20 antibody and anti-CD20-polymer conjugates (EL-4 CD-20 (transf.), biotin/streptavidin-alophycocyanin (APC) assay (100 µg AtB/mL).*

Biological Evaluations. AtB-binding activity experiments showed that antibody-targeted conjugates prepared from DTT-modified AtB had activity slightly lower than native AtB (~80% of activity of native AtB). In contrast, the conjugates prepared from ITH-modified AtB showed dramatically decreased binding activity, only up to 25% of that of native AtB (Figure 2). The cytotoxic effect of star-like antibody-targeted conjugates was more pronounced than that of the nontargeted conjugates—80% of long-time survived animals versus 20% for nontargeted animals (T-cell lymphoma EL4, therapeutic regime, treatment on the 11th day, 15 mg of DOX eq/kg, i.v.). A detailed study of *in vivo* biological activity of the conjugates is underway.

Conclusions

We have described two different methods of synthesis of star-like water-soluble antibody-targeted drug delivery systems based on HPMA copolymers, with pH-dependent drug activation. Semitelechelic Dox-bearing copolymers were attached in these conjugates to modified antibody via one-point attachment to form a star-like structure. The method of antibody modification, using ITH or DTT, strongly influenced the number of introduced reactive sulfhydril groups and binding efficacy of the conjugates to cells. All the conjugates were relatively stable at blood pH 7.4 but released the active drug under mild acidic conditions (pH 5), modeling the endosomal and lysosomal environments in the cells.

Acknowledgements

This work was supported by the Ministry of Education, Youth and Sports of the Czech Republic, through the program Research Centres (grant no. 1M0505) and by the Grant Agency of the Academy of Sciences of the Czech Republic (grant no. IAA400500806).

References

1. Etrych, T, Jelínková, M, Říhová, B, Ulbrich, K. New HPMA copolymers containing doxorubicin bound via pH-sensitive linkage. Synthesis and preliminary *in vitro* and *in vivo* biological properties, J. Control. Release 73: 89-102 (2001).
2. Ulbrich, K, Etrych, T, Chytil, P, Jelínková, M, Říhová, B. Antibody-targeted polymer-doxorubicin conjugates with pH-controlled activation, J. Drug Targeting 12: 477-489 (2004).
3. Etrych, T, Mrkvan, T, Říhová, B, Ulbrich, K. Star-shaped immunoglobulin-containing HPMA-based conjugates with doxorubicin for cancer therapy, J. Control. Release 122: 31-38 (2007).
4. Mrkvan, T, Šírová, M, Etrych, T, Chytil, P, Strohalm, J, Plocová, D, Ulbrich, K, Říhová, B. Chemotherapy based on HPMA copolymer conjugates with pH-controlled release of doxorubicin triggers anti-tumor immunity, J. Control. Release 110: 119-129 (2005). ■

Structural and Chemical Evaluation of a Lyophilised "Fast-Melt" Formulation Using Micro-CT and Raman Spectroscopy

Andrew Parker[1]

Background

Lyophilised "fast melt" formulations are increasingly becoming the method of choice for a number of solid dosage forms. This is due to increased potential bioavailability coupled with increased patient compliance. The fast-melt characteristics of these formulations are apparent due to the structural properties of the formulation, particularly the pore structure, which is formed during the freezing process and subsequently revealed after lyophilisation. Indeed, the freezing process parameters can influence further characteristics of fast-melt formulations by influencing the distribution of the formulation throughout the matrix. One consequence of this is poor taste-masking, an undesirable phenomenon that would most likely limit patient preference and compliance.

In order to reduce or eradicate these unwanted formulary aspects, it would be beneficial to understand how different processing parameters impact the material characteristics of a lyophilised solid dosage formulation at the micrometer scale. Thereby, the formulator could better understand the location of each formulation component and the subsequent abundance of each component in various regions, aiding the optimisation of the manufacturing process where applicable.

This study presents a strategy for the physical and chemical characterisation of a lyophilised product using high-resolution imaging and chemical analysis techniques. In particular, the technique of micro-X-ray computed tomography (micro-CT) enables data to be acquired non-invasively. This approach carries strong merit when examining brittle formulations such as lyophilised products, as sample preparation to reveal bulk material can potentially induce preparation artefacts.

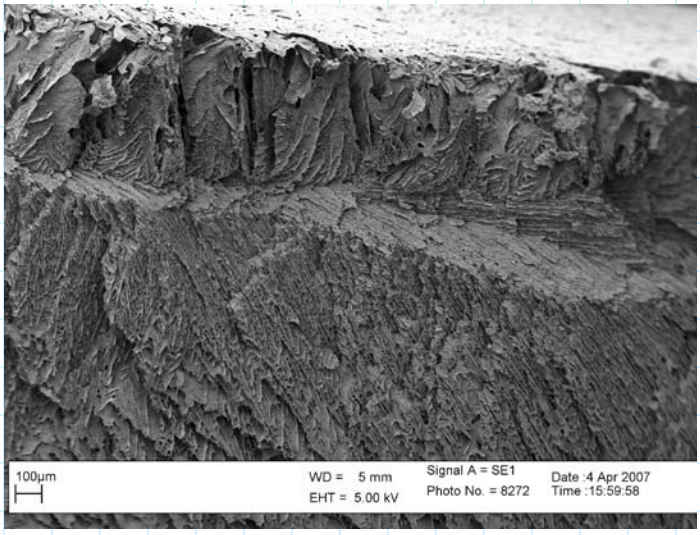


Figure 1. *SEM image of lyophilised formulation matrix.*

Methods

The fast-melt product to be analysed was an OTC medicine containing 10 mg of the active ingredient in a mannitol and gelatine matrix. Confocal Raman microscopy was employed to chemically image the formulation; the upper and lower surfaces of the formulation were imaged using a Witec CRM200 confocal microscope, at a resolution of 8 cm^{-1}. Maps were acquired from 75 µm × 75 µm regions, with a step size of 0.5 µm, giving a spatial resolution of approximately 1 µm. Meanwhile, high-resolution imaging of the formulation was carried out using micro-CT; the SkyScan 1172, employing a 20-kV X-ray source, was used to acquire images over 180 degrees with a step-size of 0.2 degrees. Complementary high-resolution imaging was performed using scanning electron microscopy; the LEO 1430v SEM was used to visually compare the morphologies of the formulation.

Results

SEM Analysis. Visual analysis of the internal micro-structure of the formulation by SEM revealed a high degree of anisotropy in the size and shape of the observed features. Figure 1 illustrates these structural and morphological differences. Closer inspection (captured in Figure 2) elucidates the presence of a fine porous structure.

Micro-CT Analysis. Non-invasive imaging of the solid dosage formulation using micro-CT revealed an open platelet-type 3-D

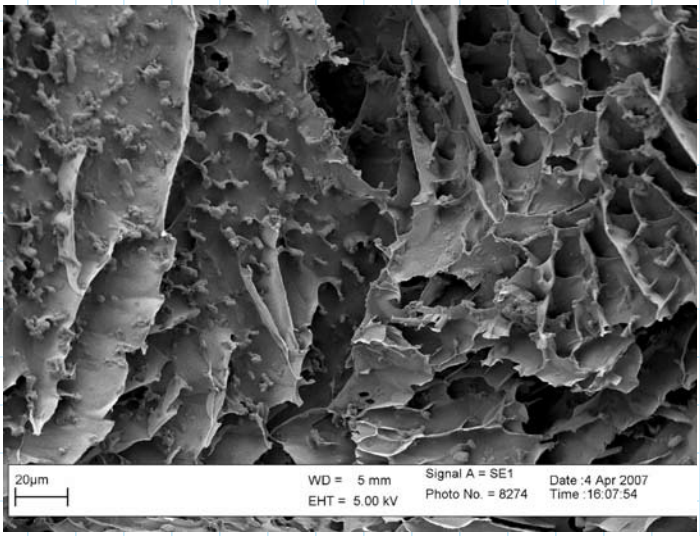


Figure 2. *SEM image of lyophilised formulation matrix shown in Figure 1 at higher magnification.*

[1] Molecular Profiles Ltd., 8 Orchard Place, Nottingham, NG7 2RD, UK. E-mail: aparker@molprofiles.co.uk.

connected network consisting of materials of at least two different densities, as shown in the binarised cross-sectional image in Figure 3. Three distinct microstructures can be resolved that contain differing levels of both matrix material and residual free volume space. All of this corresponds to the anisotropy in the size and shape of the structure observed previously by SEM (Figures 1 and 2) and can be quantified with the micro-CT data.

Upon closer inspection of these domains (captured in Figure 4A–C), the microstructures can be described in more detail:

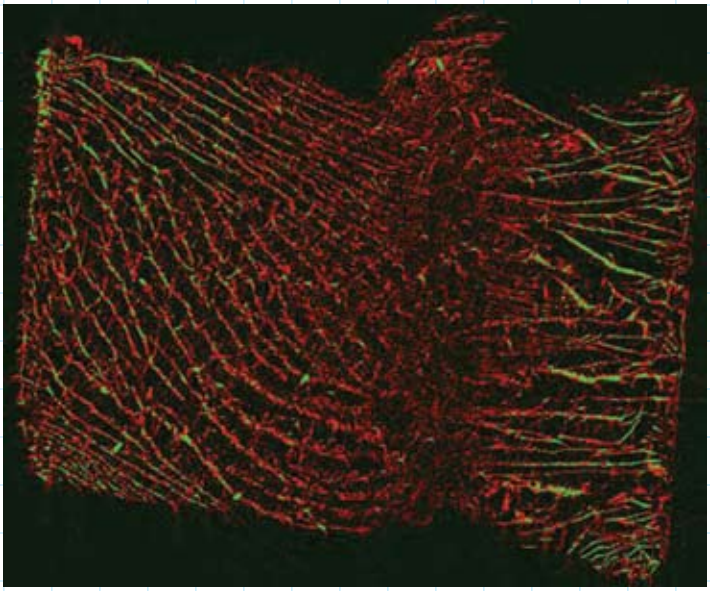


Figure 3. *Reconstructed, binarised cross-sectional slice of the lyophilised formulation. The green areas relate to the presence of the drug, whereas the red areas relate to the excipient and the black areas within the sample represent pores.*

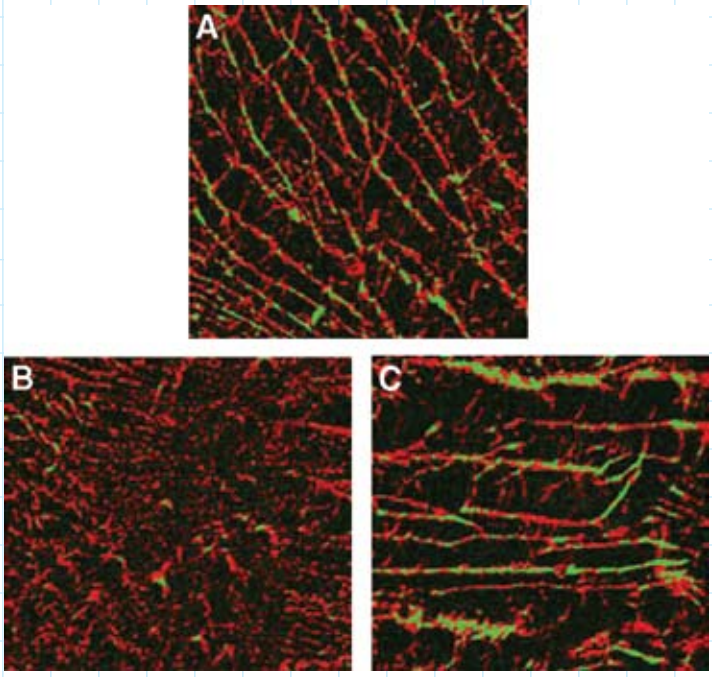


Figure 4. ***A,*** *CRM image of microstructure A;* ***B,*** *CRM image of microstructure B; and* ***C,*** *CRM image of microstructure C.*

- Microstructure 1 (Figure 4A) consists of a fine matrix network with a high residual free volume space. Calculations show that there is approximately 15% matrix material with 85% pore volume space.
- Microstructure 2 (Figure 4B) consists of a porous network with a relatively high degree of connectivity and tortuosity. Calculations show there is approximately 25% matrix material and 75% pore space.
- Meanwhile, Microstructure 3 (Figure 4C) consists of a porous network with lower connectivity and tortuosity relative to microstructure 2. Calculations show there is approximately 22% matrix material and 78% pore volume space.

CRM Analysis. Confocal Raman chemical mapping was performed on the upper and lower surfaces of the lyophilised formulation. Figure 5 illustrates the results. This approach identified the presence of the drug substance and mannitol in the amorphous state in both surfaces of the formulation. The distribution of the drug within both the upper and lower surfaces of the formulation correlates to the distribution of the highest density material observed by micro-CT and shows that the drug particles are discrete and less than approximately 10 µm. The spectra acquired from the upper and lower surfaces of the tablet also revealed heterogeneity in the relative distribution of the

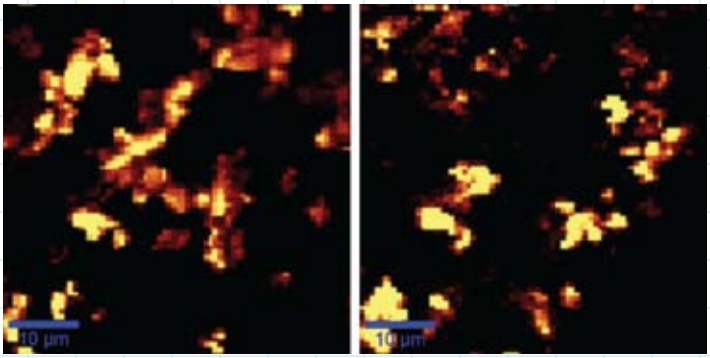


Figure 5. *Confocal Raman images of the distribution of the active ingredient within the matrix. Left: upper side of formulation; right: lower side of formulation.*

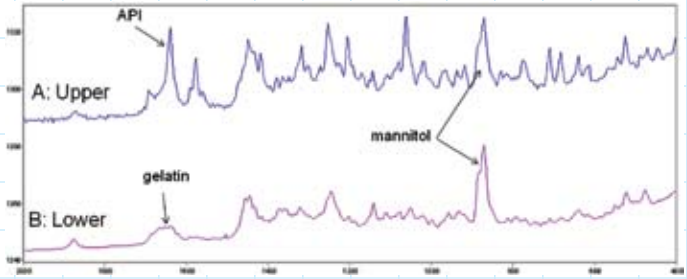


Figure 6. *Averaged Raman spectra extracted from the mannitol areas on the maps from the upper (A) and lower (B) surfaces of the tablet, showing mannitol and the drug substance in the upper side and mannitol and gelatine in the lower side.*

Scientifically Speaking—Parker continued on page 14

Scientifically Speaking—Parker continued from page 13

excipients with respect to the drug substance. On the upper side, the mannitol was predominantly located with the drug substance at the micrometer scale, whilst on the lower side of the tablet the mannitol was mainly separated from the drug substance and colocated with the gelatine on the micrometer scale (Figure 6).

Conclusions

Micro-CT and confocal Raman microscopy are powerful techniques for the non-invasive analysis of lyophilised formulations. Micro-CT is capable of imaging the entire sample at high resolution, producing images that are independent of any sample preparation artefacts. In addition we are able, through the use of image analysis, to quantify the observed components within the micro-CT images. In conjunction with confocal Raman microscopy we were able to identify the size and distribution of the excipient and drug material within the lyophilised formulation. Collectively, this enabled the heterogeneity of the formulation to be better understood and could provide an important analytical strategy for the formulator in improving their understanding of the relationships between processing parameters and formulation microstructure. ■

Thank You for Your Years of Service to CRS!

David Brayden

Marcus Brewster

Susan Cady

Igor Gonda

Betina Martinez

Sevda Senel

Ronald L. Smith

Arthur Tipton

Roderick B. Walker

Development and Regulatory Challenges for Controlled Release Formulation

CRS/AAPS Workshop • November 7–8, 2009
Los Angeles Convention Center • Los Angeles, California U.S.A.

Workshop Chairs

Ron Ortiz, Upsher-Smith Labs, U.S.A.
Dody Reimer, Northern Lipids, Inc., Canada
Louise Rosenmayr-Templeton, Tower Pharma Consulting, Austria
Avinash Thombre, Pfizer, Inc., U.S.A.

Educational Objectives

- To provide an understanding of the developmental and regulatory challenges for controlled release formulations utilizing mature and evolving new technologies in Europe and North America
- To provide a venue for young and/or established scientists to informally meet with other scientists and regulatory authorities
- To share and discuss fundamental science and experiences that may be of value to individuals dealing with various CR technologies
- To gain an understanding of the differences between the regulatory bodies of the E.U. and the FDA
- To increase an individual's knowledge about a variety of controlled release technologies that may not be found in the literature through shared experiences and panel discussions
- To apply newly acquired knowledge and a suitable approach to the potential design of the attendees own pharmaceutical products

Topics

Carrying out Early Phase Clinical Trials in the European Union on Non EU Produced Investigational Medicinal Products: Importation and Qualified Person Certification Challenges
Controlled Release and Immunogenicity—A Vaccine Perspective
Development and Regulatory Challenges Associated with the Transdermal Delivery of Small Molecules
Development of Orally Disintegrating Tablets
Developmental and Regulatory Challenges with Interferon Microparticles
Developmental and Regulatory Challenges with Liposomes
Developmental and Regulatory Challenges with RNAi Therapeutics
Intracutaneous Drug Delivery: Considerations Developing a New Combination Drug Product
The Development History of NanoCrystal® Products: A 10 Year Perspective
The Regulatory Challenges during the Development of Risperdal Consta—A Long Acting Injectable
The Science and Regulatory Perspectives of Controlled Release Products with Emerging Technologies

Invited Speakers

Richard Green, Pfizer, U.K.
Kris Hansen, 3M, U.S.A.
Kevin Harper, Sanofi-Pasteur, Canada
Michael Horstmann, LTS, Germany
Elaine Liversidge, Elan Pharmaceuticals, U.S.A.
Aidan Madden, FivePharma, Ireland
Patrick Marroum, FDA, U.S.A.
Sara Nochur, Alnylam, U.S.A.
Michael Palmieri, Alkermes, U.S.A.
Tom Redelmeier, Northern Lipids Inc., Canada
Laurens van Pinxteren, OctoPlus, The Netherlands

Workshop Registration

CRS members can register at the AAPS member rates. Register by September 11, 2009, at www.aapspharmaceutica.com/annualmeeting for the best rates.

Registration rates include two days of programming, with coffee breaks and two lunches. The registration fee does not include breakfast.

Photo courtesy of Tom & Michele Grimm.

Use of Slow-Release Implants to Manage Fertility in Marsupials

Dr. Doug Eckery[1]

Effective management of mammalian wildlife and pest species is becoming increasingly necessary throughout the world. In Australia and New Zealand a number of marsupial species require management because of the negative impacts they have on biodiversity, spread of disease, and agricultural production or because they have become overabundant due to habitat loss or other disruptions to the environment. In Australia, the most actively managed species are kangaroos, wallabies, and koalas (1). The brushtail possum was introduced into New Zealand to establish a fur industry, but it has now become the most significant vertebrate pest both ecologically and economically. Its population is estimated to be 50–70 million. Conventional methods of control, such as poisons, trapping, and shooting, are very effective at a local scale, but the environmental, trade, public acceptance, and cost risks associated with poisons may create difficulties for their continued long-term use. In Australia, the culling of animals, especially of iconic species, such as kangaroos and koalas, generates a lot of negative reaction and presents wildlife managers with numerous challenges. This has resulted in research being undertaken to improve existing methods or to develop new methods to reduce the fertility of animals. Fertility control has long been considered an attractive alternative to lethal control, largely because it is thought to be more humane and have greater potential to be species specific.

Work in marsupials to disrupt the actions of reproductive hormones has involved the use of long-acting contraceptive implants or vaccines. The implants that have been tested have contained either synthetic progestins or gonadotrophin-releasing hormone (GnRH) agonists. Treatment with a GnRH agonist initially induces an increase in circulating gonadotrophins from the pituitary gland, but chronic treatment causes down-regulation and desensitisation of the pituitary gland, which suppresses the synthesis and secretion of gonadotrophins (Figure 1), leading to inhibition of ovarian follicular development and ovulation in females. For studies in marsupials, the most commonly used GnRH agonist has been deslorelin (D-Trp6-Pro9-des-gly10-GnRH ethylamide [Figure 2]), which is formulated into implants (Suprelorin®, Peptech Animal Health Pty. Ltd., Macquarie Park, NSW, Australia). The implants were initially developed as an ovulation-inducing agent in mares and subsequently for the suppression of reproduction in domestic dogs and cats (2). The implants release deslorelin from a matrix consisting predominantly of low melting-point lipids and biological surfactant. Each implant is 2.3 mm in width and 12.5 mm in length and contains 4.7 mg of deslorelin, which is placed subcutaneously between the shoulder blades using a single-use implanting device (Figure 3). In a real-time dissolution assay, the implants released doses of >1 µg/day for periods of >1 year. The *in vivo* release rates of deslorelin in the marsupials that have been tested are unknown; however, effective control of fertility has been achieved in each species for at least one year (3–6). In all cases, animals have returned to full fertility after withdrawal of the implants, and no side effects have been noted.

The cost of any fertility control operation depends on both the cost of the contraceptive agent and the cost of delivering it to the animals. The effective delivery of any reagent in a field situation

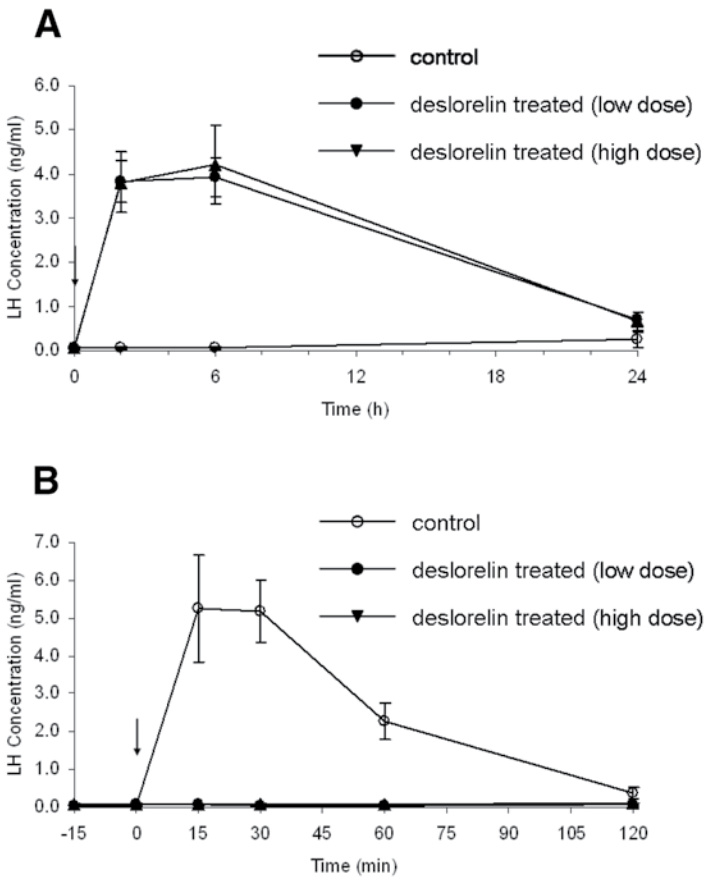


Figure 1. *Effects of the GnRH agonist deslorelin on plasma LH concentrations in female brushtail possums.* ***A)*** *Initial increase in LH after insertion of deslorelin implant.* ***B)*** *Lack of response to a GnRH challenge in treated animals 9 weeks after insertion of implant demonstrating downregulation of LH. Modified from Eymann et al. (3).*

[1] School of Biological Sciences, Victoria University of Wellington, Wellington, New Zealand.

is complicated and involves a number of considerations, from the physiology of the target and non-target animals to the pharmaceutical characteristics of the formulation (7). Moreover, the use of deslorelin implants requires physically catching the animals, and in some cases (e.g., possums) anaesthesia, to apply the treatment. This makes application of the implants labour-intensive and raises questions about the feasibility of the method for large-scale treatment of populations. To overcome the need to capture animals, methods of remote delivery are currently being investigated.

Ideally, a fertility control reagent for management of wild populations would cause permanent sterility from a single dose. Thus, at present another major limitation to the use of these implants for large-scale population control is the length of time they are effective. With the current formulation, implants need to be administered on a yearly basis to ensure suppression of reproduction. In marsupials that live from 5–12 years, the costs involved in recapture or even finding each animal on a yearly basis would be cost prohibitive. For large-scale management, longer acting formulations that lend themselves to remote delivery are needed.

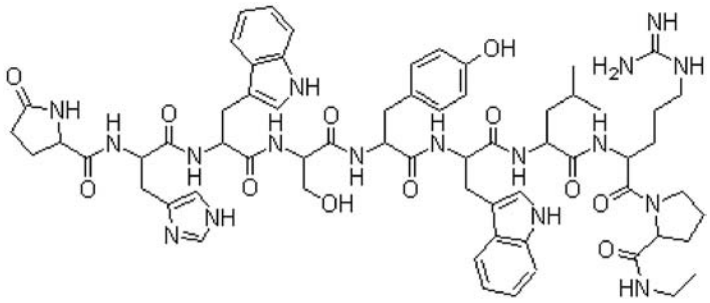
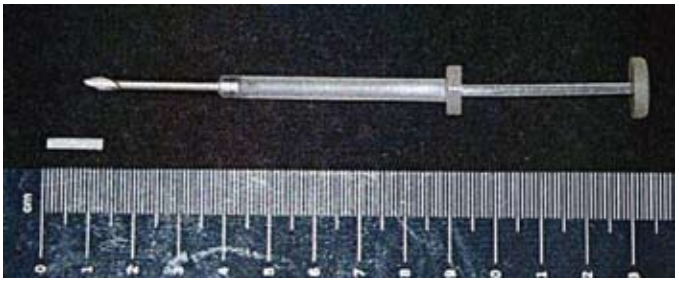


Figure 2. *Structure of the decapeptide, deslorelin (Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-NHEt).*



Figures 3. *Deslorelin implant and single-use implanting device.*

On the other hand, to manage fertility in captive or semi-captive animals (e.g., wildlife parks, botanical and zoological gardens, and small islands) the use of implants is much more feasible. Moreover, reversibility and temporary infertility are sometimes desired.

Although the goals for managing fertility differ between species, and even between countries, results from studies on marsupials provide evidence that reproduction in females can be inhibited through disruption of GnRH. Slow-release GnRH agonist implants can be a useful management tool, especially for populations in small, localised areas. The development of longer-acting formulations and methods of remote delivery deserve further attention to investigate their use for managing fertility in marsupials.

References

1. Herbert, CA. Koalas and kangaroos: Managing Australia's charismatic icons on the world's stage, Proc. 22nd Vertebr. Pest Conf., RM Timm and JM O'Brien, eds., University of California, Davis, pp. 17-22 (2006).
2. Trigg, TE, Wright, PJ, Armour, AF, Williamson, PE, Junaidi, A, Martin, GB, Doyle, AG, Walsh, J. Use of a GnRH analogue implant to produce reversible long-term suppression of reproductive function in male and female domestic dogs, J. Reprod. Fertil. Suppl. 57: 255-261 (2001).
3. Eymann, J, Herbert, CA, Thomson, BP, Trigg, TE, Cooper, DW, Eckery, DC. Effects of deslorelin implants on reproduction in the common brushtail possum (*Trichosurus vulpecula*), Reprod. Fert. Dev. 19: 899-909 (2007).
4. Herbert, CA, Trigg, TE, Renfree, MB, Shaw, G, Eckery, DC, Cooper, DW. Long-term effects of deslorelin implants on reproductive success and plasma progesterone and LH concentrations in the female tammar wallaby, Reproduction 129: 361-369 (2005).
5. Woodward, R, Herberstein, M, Herbert, CA. Fertility control in female eastern grey kangaroos using the GnRH agonist deslorelin. 2. Effects on behaviour, Wildlife Res. 33: 47-55 (2006).
6. Herbert, CA. Contraception of marsupials using slow release implants containing the GnRH agonist deslorelin, Ph.D. thesis, Macquarie University, Sydney, Australia (2002).
7. McDowell, A, McLeod, BJ, Rades, T, Tucker, IG. Application of pharmaceutical drug delivery for biological control of the common brushtail possum in New Zealand: A review, Wildlife Res. 33: 679-689 (2006). ■

UKICRS Symposium 2009: Translating Pharmaceutics into Therapeutics[1]

Noosh Daneshpour, Malou Henriksen, Jubair Hussain, Daniel Kirby, Sarah McNeil, and Randip Kaur
Aston University, Birmingham, U.K.

The 2009 UKICRS Symposium was held Wednesday, April 1, 2009, at King's College London. This year our annual meeting looked at translating drugs into medicines, and we called upon a range of experts to share their thoughts on the challenges and tribulations of such work. It was a great meeting, and we had more than 80 attendees, which gave us a lively atmosphere and plenty of discussions.

Left to right: Sam, Vitaliy, Woei Ping, and Aleksandra from the UKICRS committee are ready to meet our members at the registration desk.

Opening the meeting, Tudor Arvinte (chief executive officer, Therapeomic Inc. and Department of Pharmaceutics and Biopharmaceutics, School of Pharmacy Geneva-Lausanne, University of Geneva) discussed the overarching challenges of translating biological molecules into medicines. He noted that we are not in a good place pharmaceutically right now; looking at the number of ongoing human clinical trials, there are at present ~2,000 biologicals in human studies, with only ~600 in phase 3. Of these, perhaps two or three will make it. Taking into account the processes from bench to product, Tudor considered that what is missing between the drug and its manufacture are the physics and biophysical properties of the drug. When we speak about formulation we often think of stability, and indeed often the less we know about the physical and chemical properties of a biological, the more stable we think it is. However, often the tests we do is dictated by the tools we have. Tudor noted that we need to adapt our methods to the needs of the formulation and not to the needs of the analytical techniques.

Our first speakers of the session – Tudor Arvinte (left) and Brij Patel (right).

Our second speaker of the morning was Brij Patel (MHRA), who considered "Drug Delivery: From Laboratory to Licensure—Regulatory View." Brij presented a very nice series of case studies on novel delivery systems and devices that have been licensed. Examples included the oral Oros system, which offers prolonged release of the drug, as the water seeps into the system the drug is pumped out; Mutaflor, which is a lyophilised preparation of viable *E. coli* strain in an enteric-coated capsules; and ZinaJet 2, which is a "cool-click" needle-free device. Brij then highlighted the key points in developing a regulatory dossier, and a helpful way through this is to have an open dialog with the regulators as early as possible to ensure all appropriate assessments and studies are considered. For example, what are the critical steps in the manufacturing processes, what is the ID testing for each component, and does this test work in a multi-component system reliably? Also, as the product evolves do you have comparability—as site transfers, scale up, concentrations, and sources may change?

Our members enjoying some networking.

After the break, Chris McGuigan (Cardiff University) discussed "persuading phosphates to enter cells." In the persuasion of phosphates to enter living cells, making small changes to nucleosides can achieve a therapeutic effect for drug

[1]Reproduced from the *UKICRS Newsletter*, 2009.

delivery. More specifically, for example, the cancer drug Clorfarabine was the first drug of its kind to be carried through from research to the clinic for childhood leukaemia. This works based on the phenomenon that the administered drug is always inactive until phosphorylation occurs to create an active species. However, there are disadvantages with the use of nucleoside drugs, as they are poorly metabolised, rapidly deactivated, require active transport, and have associated toxicity. To counter such problems, monophosphates or ProTides (phosphate pro drugs) can alleviate such issues, as they are an activated form of the phosphate that are phosphate disguised and lipid soluble, which are designed to fall inside the cell and desirably have non-toxic by-products, whilst achieving more rapid hydrolysis within target cells. Overall, ProTide methods can enhance the potency and selectivity of nucleoside drugs.

From left to right: Ian Robertson, Chris McGuigan, and Ed Lavelle.

The importance of adjuvants for enhancement of the immune response to recombinant protein and DNA vaccines was highlighted in Ed Lavelle's (Trinity College, Dublin) talk entitled "Delivery Systems for Injectable and Mucosal Vaccines." Key topics discussed included "inflammasomes" (multi-protein complexes with known caspase 1 and 5 stimulating properties), the use of TLR ligands and plant lectins as adjuvants in injectable and mucosal adjuvants, respectively, and the intracellular signalling cascades associated with these adjuvants. The roles of dendritic cells was highlighted, in particular their stimulating effects on Th-17 cells, with the subsequent release of Th-17, a relatively new cytokine with roles bordering both innate and acquired immunity. Of the mechanisms of action attributed to adjuvants, the "danger effect" hypothesises that a certain amount of tissue damage is necessary to enhance immunostimulatory responses to administered antigen. In relation to this, administration of TLR agonists such as Poly:IC, LPS, and other commonly derived bacterial components, phagocytosis, and strong IL-1 responses have been noted. Furthermore, the increased uptake and augmented immune responses to particulate antigen, as opposed to soluble antigen, suggest that physical similarities to the pathogen itself may also play a role in the stimulatory abilities seen with many adjuvants. Whilst injectable adjuvant-containing vaccines support the danger theory, mucosally administered vaccines must rely on a different method of action. Poor uptake and transport across the cell bilayer, poor T-cell presentation, and inefficient antigenic protection from mucosal enzymes are all problems hindering the development of successful mucosal vaccines. The importance of dendritic cells in the uptake and presentation of antigen peptides is highlighted by the lectin UEA-1—combination of UEA-1 in a particulate system leads to dendritic cell uptake and IL-1α and β enhancement. Focussing on chitosan as a further adjuvant, knock-out mice studies showed IL-1 production by dendritic cells with the consequential production of Il-17. Both adjuvants induce Th1/Th17-based actions, which are key extracellular pathogens. To summarise, whilst the presence of antigen is necessary for successful adaptive immunity, the use of a delivery system and/or adjuvant is known to specifically modulate the type and efficiency of the innate immune response encountered.

Ian Roberston (Colorcon) discussed the trends in modified release products and provided a comparison between releasing hydrophilic drugs from matrices versus multi-particulates (MP) in terms of strengths and weaknesses. The presentation started with industrial aspects and commercialization of different dosage forms and continued with a FDA approval summary, concluding that oral solid dose with 58% of 22,000 approvals overall are predominant, and modified release (MR) product sales are global, with large markets in North America, the EU, and Asia. Then, there was a comparison of extended and delayed release of MR tablets versus different multi-particulates (MP), where tablets remain dominant but with MP playing a significant role. It was also concluded that drug release across a water-insoluble membrane according to Fick's first law of diffusion and modulation is achieved using pore formers. After that, there was a discussion about formulation design and pharmacokinetic and manufacturability considerations for both MP and matrices. Overall, it was stated that there is no single technology that meets all drug and clinical challenges; however, risk-based design can facilitate quality dosage form development.

Christian Seiler (Merck, Sharp ad Dohme) opened the afternoon session with a look at the design and evaluation of oral extended-release dosage forms based on compound and technology attributes from an early development perspective. A number of factors need to be considered when dealing with extended-release systems, including the kinetics of the release and pharmacokinetic parameters of a drug and type of release system and formulation used. Early studies have revealed that modelling often gives valuable but sometimes conflicting results.

The second presentation of the afternoon session saw Prof. Ijeoma Uchegbu (London School of Pharmacy) describe, from experience, the translation "from nanoscience musings to a possible medicine." Citing the case study of chitosan-based amphiphilic polymers, which self-assemble when in solution at very low concentrations to form stable complexes with the ability to entrap hydrophobic drugs, such as griseofulvin and cyclosporine, this session highlighted the extensive characterisation that must be performed on several aspects of the drug delivery system before being applied in the clinical setting. For example, it was necessary to fully elucidate the exact

UKICRS Symposium 2009 continued on page 20

UKICRS Symposium 2009 continued from page 19

From left to right: Christian Seiler, Ijeoma Uchegbu, and Andrew Ingham

mechanism of increased oral absorption of hydrophobic drugs yielded by the use of these nanoparticles, with results presented demonstrating that factors other than the increased solubilisation of the drug played a significant role. Indeed, it was shown that the nanoparticle formulation had an effect on both the dissolution and the transcellular transport of the drug, whereas paracellular transport and p-glycoprotein efflux pump inhibition were not factors in the observed increased bioavailability. In addition, it was also shown that the bioadhesive nature of the polymer increased the residence time of the drug at the site of absorption. Further, the polymer itself had to be rigorously characterised in order to produce a monograph for quality control and analysis purposes, requiring each step in the polymer synthesis (acid degradation, palmitoylation, and methylation) to be validated and shown to be reproducible, as well as the thermal properties of the drug. All of this characterisation was required in addition to the "conventional" dosage form tests of dissolution rate, stability, and quantification of free and bound polymer levels within the formulation, proving that the translational steps between "basic" research and its clinical application are perhaps more complex and intricate than they seem at first sight.

Dr. Andrew Ingham (Aston University, Birmingham, UK) provided a comprehensive overview on the "Optimisation of Biotechnology Formulations for Freeze-drying Storage." The presentation focussed on the use of thermal probes to monitor various stages throughout the freeze-drying process. Although the appearance of the freeze-dried cake apparently does not matter regarding stability, it seems that medics disregard and return a higher percentage of collapsed cakes back than "good looking" cakes; therefore, it is more desirable to generate good freeze-dried cakes. Freeze-drying consists of various stages: freezing, primary-drying, and secondary-drying, whereby the product converts through various phases, starting off as a liquid converting to a solid, through freezing, to a gas by application of a vacuum and an increase in temperature. Thermocouples, placed within the centre of the samples, are used in order to effectively monitor the temperature changes of the sample and the shelf and condenser of the freeze-drier throughout the process to predict the end point of each freeze-drying stage, in order to ensure the product is completely dried. Although this is effective on a small scale, it is more difficult to control and monitor at an industrial scale. One possible solution to this problem was addressed through the application of mechanical monitoring, where the probe can be placed at the bottom of the vial. Although this method of monitoring was found to be better than the thermocouples, this procedure was still not ideal, as it was shown that the end point of primary drying was still not fully predicted and could still be improved. Therefore, thermal pickups that can be controlled through remote control and avoid human contact are being investigated and developed.

Clare Hoskins (School of Pharmacy, University of Hertfordshire) presented her work on the fabrication of novel nano-sized polymeric micelles for drug delivery. The background to the presentation was the use of amphiphilic polymers to increase the solubility and efficacy of hydrophobic drugs. Two amphiphilic comb-shaped polymers were synthesised by grafting PAA (15 kDa) with 5% mol hydrophobic pendant groups, D-AA and F-AA. The particle sizes of these aggregates were at 6 mg/mL^{-1}, 224 nm for D-PAA and 91 nm for F-PAA. The CAC value for D-PAA was 0.187 mg/mL while, F-PAA showed two CAC values (0.4 and 1.5 mg/mL). Overall, it was found that encapsulation of propofol in polymeric self-assemblies improved the propofol aqueous solubility by 90- and 3.4-fold. In addition, the study demonstrated the use of the amphiphilic polymers as delivery systems for hydrophobic drugs and indicated the type of hydrophobic pendant groups has a significant influence on drug solubilising capacity.

Poster winners James Mann (left) and Daniel Kirby (right).

Malou Henriksen (Aston University) outlined her work on the biodistribution of liposome-based vaccines. Using duel radio-active markers, Malou was able to track the fate of both the liposome carriers and the sub-unit antigen after injection. Her work showed that the cationic liposomes were able to form a depot effect, retaining both the cationic liposomes and their antigen at the site of injection for up to 14 days, whilst "free" sub-unit antigen injected without a cationic liposome delivery system was cleared rapidly from the body. Overall this would suggest that the highly strong vaccine adjuvant profile of the cationic liposomes tested was in part related to this strong depot

effect, as parallel studies using neutral liposomes that did not form a depot effect showed low vaccine efficacy.

Closing the conference, Peter York (University of Bradford) presented "From Particle Engineering to Pharmaceutical Products—A Supercritical Experience." Supercritical fluid technology is now recognised as offering key advantages in particle engineering for drug delivery. The necessity of a uniform particle size with defined solid-state properties and predictable drug release profiles are all key factors for therapeutics but not always easy to achieve. The processes developed by Prof. York and his team were able to achieve this, and through this, the research was translated into a product and many academics were translated into a company through the hard work and commitment of the team.

Post-graduate speakers Clare Hoskins (left) and Malou Henriksen (right).

Closing the meeting, Yvonne Perrie announced the winners of our two poster prizes (complimentary registration to the CRS Annual Meeting in Copenhagen) as decided by our panel of judges. Congratulations go to James Mann from MSD and Daniel Kirby from Aston University. ■

Inaugural SFI Irish Drug Delivery Network Conference (with UKICRS): Optimising Drug Delivery

The inaugural conference of the SFI Irish Drug Delivery Network (IDDN) Strategic Research Cluster will be held at University College Dublin, August 19, 2009. This one-day conference will bring together leading principal investigators from the Science Foundation Ireland (SFI)-funded IDDN cluster with select, invited international speakers on the topic of novel advanced technologies and assessment systems of drug delivery.

The conference is designed to increase the networking capacity of IDDN through co-sponsorship with the UK-Ireland Chapter of the Controlled Release Society (UKICRS). Topics to be discussed include polymeric peptide conjugates for oral delivery, modified cyclodextrins for siRNA delivery, transdermal delivery with microneedles, and *in vitro* models of pulmonary delivery, as well as a review of the current status of gene delivery vectors.

Funding for the meeting is provided by a UCD Seed Funding Award. Lunch, tea and coffee, closing reception, and a delegate pack will be provided. To save, register by August 1. For more information, visit www.ucd.ie/iddn/ or contact Dr. Graham Armstrong, Rm 255 Veterinary Sciences Centre, UCD Belfield, Dublin 4, Ireland (Tel: 00353 (0)17166017; E-mail: graham.armstrong@ucd.ie). ■

Exocharmic Science Demonstrations..

All the links in this list can be accessed directly t

Attention spans aren't what they used to be. Today, if you can remain focused for 20 minutes during the "after-lunch lecture" before the customary head bobbing kicks in, you've either been drinking way too much coffee or your BLT sandwiches were laced with amphetamines. In a brave attempt to enliven even the dullest lecture, Bodner encourages the use of "lecture-based demonstrations," nothing spectacular or dangerous, you understand, but just a light dusting of surprise to stimulate the synapses. Of course, in the lofty world of the educationally enlightened, the banal term "lecture demonstrations" doesn't really cut the mustard, and so such demonstrations are formally known by the rather more grandiose "exocharmic demonstrations" (from the Greek meaning "to exude charm"). (In the same way that some people insist that they're having "poussin" for dinner, rather than common or garden "chicken"…yeah, we know your type!)

Well, UKICRS has come up trumps again—we have undertaken the arduous task of trolling through hours and hours of YouTube clips to bring you our top 10 favourite video clips to add that little bit of spice to your lectures and presentations. Enjoy our exocharmic extravaganza!

1. The PCR Song (www.youtube.com/watch?v=x5yPkxCLads)
The PCR song was voted top of our list. Great for a sing-along, it teaches the basics of PCR. Many thanks to our friends at NZCRS for sending us this one. Come on, log on, get your lighters out and boogie on down to the PCR song: "PCR when you need to detect mutations, PCR when you need to recombine, PCR when you need to find out who the daddy is, PCR when you need to solve a crime." It really doesn't get any better than this! (No, really…we mean it.)

2. BRAINIAC Science Abuse—John Tickle Walks on Custard
(www.youtube.com/watch?v=BN2D5y-AxIY)
Always a favourite, non-Newtonian fluids. Here we have everyone's favourite Big Brother output (now star of BRAINIAC), John Tickle, walking on a swimming pool of custard.

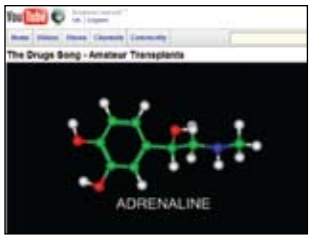
3. A pool filled with non-Newtonian fluid
(www.youtube.com/watch?v=f2XQ97XHjVw)
Not be outdone, here is the official non-British version—much more exciting. In this clip, they use cornstarch in a much deeper tank. Rock-n-roll!

4. GTCA (www.youtube.com/watch?v=ENjIZxryci8)
Another classic! The BioRad GTCA video, a worthy sequel to the PCR song. It even comes with subtitles for extra educational value.

[1] From UKICRS.

.or Just Some Funny YouTube Clips?![1]

hrough the UKICRS website (www.ukicrs.org).



5. The Drug Song (www.youtube.com/watch?v=KXROnzpsrlg)
Continuing the musical theme, here's The Drugs song by Amateur Transplants. It's fast, it's furious, and it's bonkers! [Warning: there's an expletive at the end.]

6. It's Too Late to Apoptize (www.youtube.com/watch?v=mHOX43-4PvE)
The singing is well dodgy, but it is funny and again comes with subtitles and the odd PowerPoint slide. The p53 suppressor gene makes its screen debut.

7. The Elements Song (www.youtube.com/watch?v=SmwlzwGMMwc)
For the purists amongst you, we also have The Elements song by Tom Lehrer. Actually, this is the original song of which The Drugs song is a parody.

8. "Sweet Home Apparatus"—The Ultimate Golgi Music Video (www.youtube.com/watch?v=cnK7RT1q0bA)
Some people really have too much time on their hands! If you want to know about the Golgi apparatus, this is the video.

9. Pharmacy Respect (www.youtube.com/watch?v=sGip7x-sIuo)
A humorous take on the Aretha Franklin song Respect. The funniest part is at the beginning, where the new pharmacist faces an onslaught from nurses and doctors who do not appreciate her new clinical role. Best *not* to show this video to new pharmacy undergraduates…give them four years of blissful ignorance.

10. Photosynthesis ROCKS! Take 2 (www.youtube.com/watch?v=MTBz1ggO2ro)
This is wrong on so many levels—even before we get off the title. It's basically a PowerPoint presentation set to a musical backing track. Just imagine if this approach was mandatory for all conference oral presentations….

References

Hurd, PD. Active learning. J. Pharm. Teach. 7: 29-47 (2000).

Bodner, GM. Why lecture demonstrations are 'exocharmic' for both students and their instructors. J. Chem. Educ. 5: 31-35 (2001).

Back to Basics: Dissolution Testing 1: Apparatus Overview

G. Bryan Crist[1] and R. B. Walker[2]

This is the third in a series of articles introducing the basics of aspects of research techniques that may be required for the development and evaluation of controlled release technologies.

Introduction

This is the first in a series of articles on dissolution testing and covers basic operational information for the appropriate execution of dissolution testing to ensure reproducibility and/or reliability. Furthermore, several tips for keeping apparatus in top operating condition are provided.

Our primary intention is to provide a "back to basics" approach for conducting dissolution tests, since many analysts learn how to operate dissolution apparatus from other analysts. While the intention is that the trainer imparts only "good habits," in reality several "short-cuts" are often imparted. Any deviation or misinterpretation of the compendial requirements for a dissolution test may result in bias or variability of test results and, thus, must be avoided. We are not necessarily saying that bad habits are learned, but rather that occasionally an incorrect interpretation of the requirements of the USP or other official compendium takes place. For example, an analyst may not see the need to de-aerate the dissolution media, since many monographs contained in the USP describe the preparation of dissolution medium without this essential step. However, the physical test chapter on dissolution states, "Dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gases influence the dissolution results, dissolved gases should be removed prior to testing" (1).

The effects of de-aeration should be documented during the validation of a dissolution method to evaluate bias in test results caused by the presence of air bubbles on the surface of the vessel and/or shaft. The presence of bubbles generally causes more turbulence in the vessel, which can lead to an increase in the dissolution rate of an active compound. If an analyst tests a disintegrating dosage form without proper de-aeration of the medium, a faster release rate could be observed. This could result in the release of a sub-performance batch of tablets from the quality control laboratory, which is responsible for detecting performance issues through the conduct of a properly validated dissolution test.

The Dissolution Environment

Prior to discussing dissolution testing apparatus in detail, it is appropriate to provide an overview of the environment in which that apparatus is located and maintained (Figure 1).

At the outset, the apparatus should be placed on benches with sturdy construction and located some distance away from any sources of vibration, such as fume hoods, centrifuges, tapped density test instruments, vacuum pumps, ultrasonic baths, shaker apparatus, and mixers. Bench tops constructed of very dense material transmit vibrations over long distances, and therefore, long sections of benches should be constructed with gaps located at suitable intervals. For example, it should not be assumed that an ultrasonic bath located a meter away from a dissolution apparatus will not be used while a dissolution test is in progress. The primary purpose of an ultrasonic bath in a laboratory is to dissolve solids; if it is used during dissolution testing, it may have an adverse effect on the dissolution test.

Figure 1. *Preparing for a dissolution test.*

[1] Scientific Affairs Manager–Pharma, Varian, Inc., Cary, NC, U.S.A.
[2] Head and Dean, Faculty of Pharmacy, Rhodes University, Grahamstown, South Africa.

Figure 2. *Filtration of the dissolution sample.*

Dissolution apparatus should be placed away from benches that are connected to walls supporting heavy doors or located on the other side of stairways. As doors slam, particles located in an apparatus basket can sift out during a dissolution test. This introduces variability and may alter test results. All potential sources of vibration present outside the immediate laboratory environment must also be evaluated. Many analytical laboratories are located in close proximity to pharmaceutical manufacturing and processing equipment or high-traffic areas where product and materials are transported. In short, if you would not place an analytical balance in a location due to vibration, you should not locate dissolution test apparatus at that site.

Many laboratories have limited space available for both dissolution apparatus and peripheral equipment. The laboratory should have ample space for preparing test media without affecting the dissolution test apparatus while tests are being conducted. It is recommended that the lab have a test medium preparation station with a large volume source of purified water. The preparation of large volumes of dissolution medium may require the use of mixers, de-aeration equipment, measuring and dispensing equipment, and water baths to preheat test media. In terms of occupational safety, equipment must be available to assist analysts with moving carboy containers holding more than 25 L of media. In addition. the floors in the laboratory should be coated with a non-slip material, since liquid is routinely spilled when removing and cleaning dissolution vessels or when transferring media from the preparation area to test areas.

The Dissolution Apparatus

A dissolution test usually consists of two steps: sample preparation and analysis. A validated filtration step usually separates the sample preparation and analysis procedures (Figure 2). The filtration step must demonstrate the cessation of dissolution following the removal of un-dissolved particles and the clarification of the sample prior to analysis.

Occasionally dissolution apparatus are referred to as dissolution testers despite the fact that they do not test anything but are rather instruments used for sample preparation under precisely controlled conditions. Sample preparation commences upon the introduction of the dosage form, usually a solid oral dosage form, into the basic dissolution environment. This environment is quite simple and consists of three primary components: the vessel, the media, and an agitation element.

The dissolution environment is a simple symmetrical environment that should minimize and avoid the introduction of additional turbulence during the test. Therefore, the equipment must maintain proper agitation shaft and vessel alignment, agitation speed, and media temperature. Apparatus should be constructed to minimize the effects of vibration from internal components or external sources.

Dissolution apparatus are available from manufacturers worldwide. The apparatus should be capable of passing established performance-testing criteria outlined by compendial and regulatory agencies to ensure the accurate and precise data necessary to evaluate the performance of pharmaceutical dosage forms. Without precise control of the dissolution environment, factors such as increased turbulence may contribute to faster dissolution rates, increasing the possibility of incorrect formulation characterization during research and development or the release of sub-performing lots for distribution.

In addition to strong apparatus design and construction, routine evaluation and maintenance ensure conformance to the critical tolerances and specifications outlined by the appropriate pharmacopeia (Figure 3). Prior to use, the apparatus must be properly qualified and subjected to installation (IQ), operation (OQ), and performance (PQ) qualification procedures. Once qualified, the apparatus should not be moved or disturbed in its location.

Figure 3. *Checking physical parameters prior to the dissolution test.*

Required qualification procedures for a dissolution apparatus and its associated operation will follow in subsequent newsletter articles. In addition, topics will cover aspects of intrinsic dissolution, novel dosage form testing, compendial drug release testing apparatus, and analyst training.

It has been said that a dissolution apparatus may be compared to a finely tuned, precisely crafted violin made with the finest materials. If the violin is not played by an experienced musician, it will not make music. Similarly, no matter how well made, calibrated, and maintained a dissolution apparatus is, it must be used by an analyst who has a thorough knowledge of all aspects of dissolution testing to produce appropriate results.

Reference

1. Dissolution, U.S. Pharmacopeia, USP 32, NF 27, Vol. 1, <711> p. 268 (2009). ■

CRS Board Members—Adding New Faces and Saying Goodbye

The passing of the gavel at the D'Angleterre Hotel in Copenhagen, Denmark, will welcome incoming President Diane Burgess (University of Connecticut), incoming President-Elect Mark Tracy (Alnylam, Inc.), newly elected Vice President Martyn C. Davies (University of Nottingham), incoming Immediate Past President Lisbeth Illum (IDentity), newly elected Treasurer Debra Bingham (Valeo Partners), and newly elected Member-at-Large Ruth Schmid (SINTEF Materials and Chemistry).

At the First-timers' Greeting/Members' Meeting on Sunday, July 19, CRS will honor retiring Board members Treasurer Arthur Tipton (SurModics Pharmaceuticals) and Immediate Past President Susan Cady (Merial Limited). Having fulfilled their three-year terms on the Board of Scientific Advisors (BSA), David Brayden (University College Dublin), Marcus Brewster (Johnson & Johnson), Igor Gonda (Aradigm Corporation), Betina Martinez (Lab Pharmatrix), Sevda Senel (Hacettepe University), Ronald Smith (Merck & Co., Inc.), and Roderick Walker (Rhodes University) will also be recognized. Their contributions to CRS are appreciated.

The BSA will also welcome new members at their meeting on Sunday, July 19: Christine Allen (University of Toronto), Sandra Klein (Johann Wolfgang Goethe University), Andrew Lewis (Critical Pharmaceuticals), Ozgen Ozer (Ege University), Yvonne Perrie (Aston University), Hirofumi Takeuchi (Gifu Pharmaceutical University), and Iris Ziegler (Nycomed GmbH). As always, rotating new members onto the BSA helps to keep the hot topics at the forefront for the Society and the discussions lively.

Many thanks to all CRS members who voted in the 2009 election. The Society will be well served by these outstanding CRS leaders.

2009–2010 CRS Board of Directors

President – Diane Burgess, University of Connecticut, U.S.A.
President-Elect – Mark Tracy, Alnylam, Inc., U.S.A.
Vice President – Martyn C. Davies, University of Nottingham, U.K.
Immediate Past President – Lisbeth Illum, IDentity, U.K.
Treasurer – Debra Bingham, Valeo Partners, U.S.A.
Scientific Secretary – Ijeoma Uchegbu, University of London, U.K.
Member-at-Large – Ruth Schmid, SINTEF Materials and Chemistry, Norway
Member-at-Large – Elka Touitou, Hebrew University of Jerusalem, Israel

2009–2010 Board of Scientific Advisors

Christine Allen
Joke Bouwstra
Sandra Klein
Claudia Leopold
Andrew Lewis
Karsten Mader
Mariko Morishita
Ozgen Ozer
Yvonne Perrie
Russell Potts
Patrick Sinko
Frank Szoka
Hirofumi Takeuchi
Francisco Veronese
Iris Ziegler ■

37th Annual Meeting & Exposition of the Controlled Release Society

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

Personalized Medicines and Products for the Next Generation

Session Topics

Applications of IVIVC in Veterinary Species
Biomaterials
Blood Brain Barrier
Controlled Release for Corrosion Inhibition and Self Healing
Controlled Release of Oxygen Sensitive Materials
DNA Delivery
Encapsulation of Cells and Microorganisms
Environmentally Friendly and Biodegradable Controlled Release Systems
Hydrogels
Imaging
Intracellular Delivery
Liposomes
Medical Devices
Nanomedicines
Nanoparticles and Nanofibers for Controlled Release
New Chemistries
Non-parenteral Delivery of Biologics
Novel Material and Release Systems
Ocular
Oral Controlled Release
Oral Absorption
PEG
Peptide & Protein Delivery
Polymers in Medicine
Prediction of Drug Absorption in Veterinary Species Using IVIVC
Pulmonary
siRNA/Micro RNA
Tissue Engineering
Transdermal
Translational Medicine
Tumor Targeting
Vaccines

Photo courtesy of Travel Portland / Steve Terrill.

Welcome New Members

Shahriar Abash Zadeh
Sherief Abbas Abdel-Azeez
Mona Abdel-Mottaleb
Fusun Acarturk
Barry Ager
Hamideh Aghajani
Iman S. Ahmed
Kehinde Ajayi
Hamid Akbari Javar
Milind S. Alai
Fadil Al-Alawi
Farhan Alhusban
Hamid Ali-Merchant
Daniela Allhenn
Anshuman Ambike
Chasity Andrews
Khalid A. Ansari
Sophia G. Antimisiaris
Arnida Anwar
Daniele Araujo
Aharon Azaguri
Fahriye U. Badilli
Sang-mun Bae
Aristides Bakandritsos
Haleh Bakhshandeh
Shyam Bansal
Susan A. Barker
Rengarajan Baskaran
Romy Baumann
Patrick Baumhof
Minh-Tam Baylatry
Stefanie Bechstein
Robert E. M. Becker
Arnaud Beduneau
Mustafa Beesh
Nadja Bege
Vasily V. Belov
Yolandy Benadie
Lotta Bergman
Sara Bersani
Oliver Bley
Alexandr Bolotin
Supavadee Boontha
Laetitia L. I. J. Booysen
Annika Borde
Olaf Bork
Helene Bruyere
Philipp Buch
Till Bussemer
Luciana M. P. Campos Araújo
Flavia Carvalho
Maria A. Casadei
Denis Cecchin
Roberta Censi
Cintia M. S. Cereda
Shouchung Chao
Anumita Chaudhury
San-Yuan Chen
Jong Hoon Choi
Anne Christiansen
Amornrat Chumthong
Kyeunghwa Chun
Hesson Chung
Hye J. Chung
Wang Chung-Hao
Adriana Cirstoiu
Robert Conradi
Renata Contri
Anne-Claude Couffin
George E. Cramer
Michael Crichton
Clark J. Cummings
Lilias Currie
Carina Dahlberg
Prajakta Dandekar
Fabienne Danhier
Surajit Das
Andrei Dashevsky
Heiko Debus
Danya Decoteau
Marcel De Matas
Nunzio Denora
Eneida De Paula
Nishit Desai
Sarra De Valence
Padma V. Devarajan
Burcu Devrim
Noel Dew
Rosa Di Liddo
Slavomira Doktorovova
Maria E. Dolman
Cristiana L. Dora
Betül Dortunc
Nishit Doshi
Admire Dube
Andrea Dueregger
Chandrasekar Durairaj
Friederike Eisenaecher
Jonathan Elsner
Andre Eriksson
Hanne Evenbratt
Jacco Eversdijk
Ruth Exposito Harris
James R. Falconer
Francois Fay
Lin Fei
Ana I. Fernandes
Priscileila Ferrari
Dagmar Fischer
Sarah M. Fischer
Ian P. Flawn-Orpana
Kirk Fowers
Kevin W. Frisken
Richard Fuhrherr
Naruyoshi Fujiwara
Takeaki Furudate
Hiro Furukawa
Fariba Ganji
Shan Gao
Martin Garland
Marie Gaumet
Taraneh Gazori
Julie Gelis
Solmaz Ghaffari
Sepideh Ghiam Kazemi
Sam Gilchrist
Torben Gjetting
Richard D. Gonzalez
Mario Grassi
Torkel Gren
Gyocheol Gu
Swati A. Guhagarkar
Merve Gunbeyaz
Girish K. Gupta
Sandra Haas
Niels Hagenaars
Martin G. Hahn
Kris Hansen
Jennifer I. Hare
Kentaro Hatanaka
Robert Hauser
Vanessa Hearnden
Felicity Heath
Hwang Heejin
San Hein
Hans Helms
Malou Henriksen
Christina Hentzschel
Christophe Herkenne
Mimi Hetti
Annette V. Heydenreich
Anna F. E. Hezinger
Patrice P. Hildgen
Yi-Ping Ho
Todd Hoare
Per Holm
Jaclyn M. Hosmer
Chu-Chun Hsueh
Chi-Te Huang
Ye Huang
Yuan Huang
Sarah Hudson
Mohammed J. Hussain
Manoli Igartua
Javed Iqbal
Muhammad Irfan
Takayuki Ishii
Bela Ivan
Frank H. Iversen
John K. Jackson
Vikas Jain
Yura Jang
Mirko Jansch
Pascal Janvier
Sangok Jeon
Young G. Jo
Helene Jonassen
Susan Jones
Faron Jordan
Olivier Jordan
Joohee Jung
Thomas Kaasgaard
Sachiko Kaida
Haripriya Kalluri
Koki Kamiya
Jeong W. Kang
Soo-yong Kang
Sung Soo Kang
Aysegul Karatas
Youness Karrout
Meredith T. M. Kauffman
Randip Kaur
Jonathan L. Kaye
Claudia Kegel
Danielle Keller
Sukhdeep Kenth
Heejoo Kil
Murat Kilic
Muge Kilicarslan
Miia Kilpelainen
Ah-Young Kim
Bae Y. Kim
Cha E. Kim
Hyung J. Kim
Na H. Kim
Seong-Cheol Kim
Tae H. Kim
Yong-Hee Kim
Yu-Jeong Kim
Edward Kisak
Karen Kleberg
Poornima Kolhar
Mark Kontny
Leena-Stiina Kontturi
Kala Kotipalli
Amir Kraitzer
Sanjay Kshirsagar
Stephan Kubowicz
Dominique Lacan
Ochiuz Lacramioara
Nigel A. Langley
Nancy Lape
Kim L. Larsen
Michael Leane
Doungkamol Leaokittikul
Bodil Lebeck
Jeanne Leblond
Ashlynn L. Z. Lee
In-Hyun Lee
Kate (Yu Jung) Lee
Kathy Lee
Sangkil Lee
Sang-No Lee
Dorothee Le Garrec
Vesa-Pekka Lehto
Katharina Leithner
Jean-Francois Le Meins
Karolina A. Les
Jun Li
Li Liang
Kwang-Suk Lim
Eva Lin
Yang Liu
Julia Ljubimova
Caterina LoPresti
Louise Lyhne Iversen
Johannes P. Magnusson
Olga Maksimenko
Michele Manon
Carlotta Marianecci
Kazuo Maruyama
Snehlata Mascarenhas
Massimo Masserini
Francesca Mastrotto
Koji Matsuhisa
Jason McConville
Jin Meng
Patrick Midoux
Kyung H. Min
Jusaku Minari
Ranjana Mitra
Masateru Miyake
Elaine H. Moase
Shinichi Mochizuki
Osama Mohamed
Zohreh Mohammadi
Arash Momeni
Karine Mondon
Juha Monkare
Jukka Monkkonen
Daniela Monti
Jacqueline M. Morais
Huiling Mu
Ian S. Muir
Odonchimeg Munkhjargal
Simona Mura
Silvia Muro
Sarika Namjoshi
Madalina V. Natu
Isabel Nawroth
Bismita Nayak
Vijaykumar Nekkanti
Li V. Ng
Julien Nicolas
Carsten U. Nielsen
Ebbe Nielsen
Alireza Nomani
Pernille Nordly
Onanong Nuchuchua
John M. O'Callaghan
Schiavon Oddone
Colm O'Dowd
Paula Ofek
Injoon Oh
Johannes Oidtmann
Melek Onol
Jesper Ostergaard
Martin Overgard
Shivanand Pandey
Abhay Pandit
Nicole Papen-Botterhuis
Ah-Reum Park
Ji S. Park
Kyung Park
Mi-Ran Park
Sung-Jin Park
Wooram Park
Johannes Parmentier
Jenny E. Parraga Meneses
Nilesh Patankar
Bhaumik Patel
Samirkumar Patel
Estera M. Pawlisz
Elisabeth Peeters
Carla Pegoraro
Ching-An Peng
Andrew Penrose
Laura Pescosolido
Annette Peters
Audrey Petit
Chantal Pichon
Mauro Pignatto
Klaus Pollinger
Maria Popov
Tarl Prow
Utsana Puapermpoonsiri
Mohammad S. Qadir
Thakur Raghu Raj Singh
Ulrik L. Rahbek
Anthony Raphael
Lorena Redondo
Louise K. Refsgaard
Soenke C. Rehder
Daniela Reischl
Julius F. Remenar
Thomas Renette
Nico Reum
Joakim Riikonen
Federica Rinaldi
Douglas K. R. Robinson
Marta Roldo
Kamilla Rolsted
Jessica Rosenholm
Kristina A. Runas
Marika Ruponen
Emil Ruvinov
Maedeh Salami
Javad Sameni
Ines Saniocki
Gargi S. Sanzgiri
Federica Sarti
Yoshihiro Sasaki
Gerhard Sax
Andreas Schaedlich
Frank Schaubhut
Sandra V. Schilling
Anita Schneider
Verena Schnitzler
Peter D. Scholes
Simone Schrank
Khadija Schwach-Abdellaoui
Christian Seiler
Francesca Selmin
Beatrice Semmling
Ceyda T. Sengel-Turk
Daniel Serrano
Patrícia Severino
Srinivasan Shanmugam
Sang M. Shim
Asako Shimoda
Myung-Jin Shin
Narges Shokri
Yasushi Shono
Acarilia Silva
Hilris Silva
Kamalinder K. Singh
Pirthi P. Singh
Peter Sipos
Tina Skjorringe
Jae-Woo So
Mahmoud Soliman
Emilienne Soma
Rasmus S. Sorensen
Ana L. R. Souza
Mark C. Spoerl
Angela K. Sprunk
Barbara Stella
Mladen Stojanov
Jie Su
Astrid Subrizi
Tara Sunderland
Darren Svirskis
Michele Taborelli
Farhad Tajarobi
Tetsuya Tajika
Haruko Takahashi
Yoshida Takatsune
Silvia Tampucci
Stephania Taveira
Sibichen J. Thekveli
Kathleen Thom
Louiza Thomsen
Thilini R. Thrimawithana
Giovana Tofoli
Juan Torrado
Lorraine Trager
Mohammad N. Uddin
Celine Ulmann
Angela Valle-Gallego
George Vamvakas
Helene Van de Ven
Ethlinn Van Gaal
Inge Van Rooy
Rolf Verheul
Marieke Veurink
Claudia Vigl
Meera Vijayaraghavan
Anna Viriden
Maria Vlasova
Driton Vllasaliu
Mirko Voigt
Hendrik Von Bueren
Stephanie Wallace
Ming Wang
Nick Wang
Torsten Weiss
Klaus Wormuth
Aihua Wu
Murali M. Yallapu
Ikuko Yamane
Lin Yang
QiaoWen Yang
Takeshi Yano
Mahboobeh Yeganeh Mohammadi
Hyeona Yim
Wai L. Yip
Yuichi Yonemochi
Ran J. Yoo
Sung-Kyun You
Gwang S. Yu
Nilufer Yuksel
Kyoung S. Yun
Zhibing Zhang
Min Zhao
Jieying Zhong
Yong Z. Zhou
Giovanni K. Zorzi

CRS China Initiative Subcommittee Supports the 4th International Pharmaceutical Symposium

The 4th International Pharmaceutical Symposium, "Novel Drug Delivery Systems: Research and Application," will be held September 24–26, 2009, in Shanghai, China. The symposium is organized by the Chinese Pharmaceutical Association (CPA) and co-hosted by the School of Pharmacy, Fudan University, National Pharmaceutical Engineering Research Center; Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific; and CRS. The major objective of the symposium is to bring together experts engaged in basic research and industrial applications to promote academic exchanges and explore more opportunities for collaborations in drug delivery system (DDS) R&D.

With the rapid development and intercrossing of multiple disciplines such as life sciences, molecular pharmacy, material sciences, and informatics, more and more new technologies, devices, and functional materials have been applied in novel drug formulation, among which DDS is no doubt the hottest area. The International Pharmaceutical Symposium Series is held in Shanghai biennially. The main topics of the symposium focus on current advances and future potential in DDS R&D. At each symposium, more than 20 scientists from universities, research institutes, and pharmaceutical companies who play active roles in DDS R&D are invited to deliver plenary presentations. Approximately 450 attendees will also gather to exchange information and share the latest achievements in related areas.

For the 4th International Pharmaceutical Symposium, more than 25 speakers will be invited to give presentations as part of the honor speakers section during the first two days. The symposium will also provide a forum for young researchers, including post-doctoral and Ph.D. students, to present their latest research in DDS and extensive fields on the last day. There will also be posters and exhibitions to meet various demands.

The working languages of the symposium will be English and Chinese, with bilingual translation. For more information, please visit www.dds-china.org. ■

CRS Local Chapters—Reaching Around the Globe

Expand your local network. Become involved in a CRS Local Chapter.

Argentina Local Chapter
Australian Local Chapter
Canadian Local Chapter
Germany Local Chapter
Greek Local Chapter
India Local Chapter
Israeli Local Chapter
Italy Local Chapter
Korea Local Chapter
New Zealand Local Chapter
Nordic Local Chapter
Slovenia Local Chapter
Spain-Portuguese Local Chapter
Student Chapter Illinois
Student Chapter Johns Hopkins University
Student Chapter New Jersey
Student Chapter University of Texas
Taiwan Local Chapter
Thailand Local Chapter
Turkey Local Chapter
United Kingdom-Ireland Local Chapter

CRS
Delivering Bioactives

In the News

Compiled by Steven Giannos
Industrial Editor

May 2009

New Data Demonstrate Anti-tumor Activity for ABRAXANE® Combination Chemotherapy Regimen in Patients with Metastatic Pancreatic Cancer

Business Wire: May 31, 2009 – LOS ANGELES, Calif. – Abraxis BioScience, Inc. (NASDAQ: ABII), a fully integrated biotechnology company, has announced results from an ongoing Phase I/II clinical study evaluating ABRAXANE® for injectable suspension (paclitaxel protein-bound particles for injectable suspension; albumin-bound; 100, 125, or 150 mg/m^2) administered in combination with the standard chemotherapy gemcitabine (1,000 mg/m^2) for the treatment of patients with advanced metastatic pancreatic cancer.

In a preliminary analysis of 67 patients, investigator-assessed results showed the median survival rate for patients treated with the ABRAXANE®/gemcitabine combination was 10.3 months across all dose levels. The combination also resulted in a disease control rate (confirmed complete response [CR], partial response [PR], and stable disease for 16 weeks or longer according to RECIST criteria) of 70%: 5% of patients achieved a CR, 39% of patients achieved a PR, and 26% of patients had stable disease for 16 weeks or longer.

Study results also showed a higher response rate among patients who expressed the biomarker secreted protein acidic and rich in cysteine (SPARC) compared with SPARC-negative patients. More specifically, 80% of SPARC-positive patients (8 of 10) achieved a response compared with 36% (8 of 22) of SPARC-negative patients, (P = 0.027). These findings were presented in a poster discussion session of abstract 4525 on May 31 at the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Orlando, FL.

Pancreatic cancer can be particularly hard to treat because many patients are diagnosed after their disease has progressed. This year, more than 42,000 people are expected to be diagnosed with pancreatic cancer in the United States, and more than 35,000 people will die from the disease.

"The results of this study demonstrate that the combination of ABRAXANE® and gemcitabine is well tolerated and has substantial antitumor activity in patients with pancreatic cancer, thus warranting further evaluation in phase III clinical studies," said Daniel Von Hoff, M.D., F.A.C.P., physician-in-chief, senior investigator, Translational Genomics Research Institute (TGen); clinical professor of medicine, University of Arizona; and chief scientific officer, Scottsdale Healthcare and U.S. Oncology Research. "The 80 percent response rate observed in SPARC-positive patients may suggest that metastatic pancreatic cancer patients with high levels of the SPARC biomarker may have an increased response to ABRAXANE® treatment due to its albumin-bound delivery mechanism."

A.P. Pharma Announces Additional Restructuring Effort

Business Wire: May 29, 2009 – REDWOOD CITY, Calif. – A.P. Pharma, Inc. (NASDAQ: APPA), a specialty pharmaceutical company, has announced that it has implemented a reduction of its staff, representing approximately 34% of its work force. The actions are being taken to allow the company to provide the resources needed to continue advancing its lead program, APF530, toward regulatory approval and commercialization. APF530 is a long-acting formulation of granisetron that utilizes the company's proprietary Biochronomer™ drug delivery system. The new drug application (NDA) for APF530 was submitted earlier this month for the prevention of chemotherapy-induced nausea and vomiting (CINV).

"A.P. Pharma's recent NDA submission for APF530 was the result of the dedication of our entire team, making this reduction in our work force even more difficult," said Ronald J. Prentki, A.P. Pharma's president and chief executive officer. "Considering the continuing challenges of today's economic environment, it is necessary for us to make additional reductions to our staff as we focus the Company's resources on working towards approval of APF530 in the first half of 2010. I want to extend my thanks and gratitude to our departing colleagues and wish them the very best in their future endeavors."

Sperm-like Nano-devices May Revolutionize Drug Delivery Inside the Body

in-pharmatechnologist.com: May 28, 2009 – BOSTON, Mass. – U.S. scientists at Harvard University's Rowland Institute have described a way of making large numbers of controllable nano-propellers that, despite being at an early stage of development, may one day be used to deliver drugs. The propellers, which have a 200–300 nm wide head and a 1-µm long tail arranged in a helical, corkscrew-like structure similar to that of a bacterial flagellum, can be induced to swim in a precise manner using a magnetic field.

The researchers used the propellers to push silica nanobeads 5 µm in diameter along precise, reproducible paths using a method that they believe could be used to steer similarly sized delivery particles in the bloodstream. Peer Fischer, who co-authored the research with Ambarish Ghosh, said, "Unlike 'passive' nanoparticles that move by diffusion in the body the team's technology can be actively 'propelled' and thereby steered." Dr. Fischer explained, "Our propellers are the smallest to date and the fabrication method we use is much simpler and permits propellers to be made on a very large scale and in large numbers."

The team developed a technique that can produce about a billion propellers per square centimeter of a silicon dioxide substrate in around two hours. "We used glass (silicon dioxide) but a number of other materials can be used and so this greatly enhances the utility of these propellers and permits the examination of [the] chemical nature, and compatibility of these systems." He added that combining the active technology with "chemical attachment or use of a porous medium for the delivery of chemicals could be addressed, but clearly these applications require more basic research. Silicon dioxide as a nanoparticle is for instance used in food additives, but as far as I know the FDA has not issued any directives regarding the use of nanoparticles. Use of nano/micro-particles will require biocompatibility studies." Despite these remaining hurdles, Fischer said that the group "have received expressions of interest from industry…and are open to collaborations and proposals."

DSM Biomedical Extends Its Hydrophilic ComfortCoat™ Technology Platform with the Development of a Hemocompatible Antimicrobial Coating

Business Wire: May 26, 2009 – GELEEN, Netherlands – DSM Biomedical, a global company serving the medtech and biotech industries and part of Royal DSM N.V., has announced that it has extended its lubricious ComfortCoat™ technology platform with the design of a hemocompatible antimicrobial coating to thwart intravascular catheter-related bloodstream infections.

Approximately 80,000 catheter-related bloodstream infections occur annually in U.S. intensive care units (ICUs) and are associated with as many as 24,000 patient deaths each year. Each of these infections is estimated to have a mean attributable cost of $18,000 and an associated excess hospital stay of 12 days per episode (*Journal of the American Medical Association* [*JAMA*], 2009;301(12):1285-1287).

Several tests were previously performed with this innovative ComfortCoat™ technology, indicating bactericidal activity against *E. coli* and *S. aureus*. In addition, the other properties are equivalent to the existing ComfortCoat™ hydrophilic coating technologies that DSM Biomedical offers to medical device companies—namely an excellent lubricity and superior durability that reduces stiction and friction and results in reduced patient discomfort and tissue damage. The ComfortCoat™ hydrophilic coatings are applicable for adhesion to a variety of substrates. The initial hemocompatibility tests for this technology platform were performed by Dr. H. P. Wendel of the University Hospital Tuebingen (Germany). Based on these results, it is DSM Biomedical's strong belief that this addition to the ComfortCoat™ technology platform is well suited for central venous and intravenous catheters, including PICC catheters that come into contact with blood and may remain in the body for several days. This technology platform will be used in customized applications depending on the wishes and needs of the medical device industry.

"No doubt, intravascular catheters are indispensable to modern medicine, especially in ICUs," said John Marugg, DSM Biomedical's business manager for ComfortCoat™.

"Nevertheless, while conventional catheters provide necessary vascular access, their use puts patients at serious risk for local as well as systemic infectious complications. Healthcare institutions of course purchase millions of intravascular catheters each year. We believe that our new, advanced ComfortCoat™ formulation may help device manufacturers significantly reduce the risk of catheter-related bloodstream infections."

"Moreover, our ComfortCoat™ formulation is designed to offer other critically important benefits for intravascular catheters, including lubricity, durability and abrasion resistance," added Carola Hansen, DSM's Biomedical's product manager for ComfortCoat™. "Indeed, the advanced lubricity of ComfortCoat™ can significantly reduce the stiction and friction of medical devices, especially intravascular catheters. This feature can empower surgeons and other physicians to more easily navigate through difficult pathways in order to reach targeted areas of treatment without having to use too much force."

Medical Device companies can now request samples for testing on their devices of this ComfortCoat™ technology platform extension to assure that they have access to this innovative coating technology for intravascular catheters.

Aphios Announces Presentation of Phase II/III Clinical Trial Data on Zindol® for Cancer Chemotherapy-Induced Nausea

Business Wire: May 26, 2009 – WOBURN, Mass. – Aphios Corporation has announced that the results of a Phase II/III clinical trial of Zindol® for cancer chemotherapy-induced nausea were presented at the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO) held May 29 to June 2, 2009, in Orlando, FL. Zindol® is an enhanced ginger product.

Despite the widespread use of the 5-HT3 receptor antagonist antiemetics, post-chemotherapy nausea and vomiting continue to be reported by up to 70% of patients receiving chemotherapy. Furthermore, these antiemetics have been associated with significant adverse effects, such as sedation, extra-pyramidal side effects and hypotension (associated with dopamine antagonists), as well as headache, diarrhea, or constipation. A desirable attribute in any substitute or additional antiemetic medication is both efficacy and the absence of clinically significant adverse effects.

Zindol® is an enhanced ginger product that is standardized by the bioactive constituents of ginger, gingerols, and shogaols. Aphios' scientists and engineers utilized a proprietary polarity-guided SuperFluids™ CXF fractionation technology to establish conditions for the isolation of the active ingredients of Zindol®. The technology was then scaled up for producing large quantities of the active ingredients utilizing patented SuperFluids™ CXP manufacturing technologies. The enhanced ginger concentrate was then formulated to achieve a specific concentration of ginger bioactives with all-natural liquid excipients designed to maximize stability and bioavailability of bioactive constituents

In the News continued on page 32

In the News continued from page 31

and was encapsulated in gel capsules (LiCaps®) by Capsugel, Inc., a Pfizer subsidiary.

Researchers at the University of Rochester Medical School conducted a multi-site, Phase II/III randomized, placebo-controlled, double-blind clinical trial to assess the efficacy of Zindol® (ginger capsules) for chemotherapy-related nausea in 644 cancer patients. Cancer patients who experienced nausea were randomized into four arms: one placebo and three dose-escalation arms taking ginger capsules equivalent to 0.5, 1.0, and 1.5 g of ginger. All patients received 5-HT3 receptor antagonist antiemetics on day 1 of all cycles. Data from the clinical trial indicates that all ginger doses significantly reduced nausea, with the middle and lowest doses giving the best results. Ginger caused no side effects in this study, but patients should consult with their physicians before use.

The results of the clinical trial study, entitled "Ginger for Chemotherapy-Related Nausea in Cancer Patients: A URCC CCOP Randomized, Double-Blind, Placebo-Controlled Clinical Trial of 644 Cancer Patients," was orally presented and discussed on Saturday, May 30 during the Patient and Survivor Care session of ASCO.

Aphios Corporation is a biotechnology company that is developing enabling technology platforms, including nanotechnology drug delivery platforms such as phospholipid nanosomes, biodegradable polymer nanospheres, and protein and crystal nanoparticles for the improved delivery and targeting of poorly water-soluble anticancer drugs, therapeutic proteins, and siRNA molecules, as well as enhanced therapeutic products for health maintenance, disease prevention, and the treatment of certain cancers, infectious diseases, and CNS disorders.

Emisphere Technologies Reports Encouraging Data from an Independent Clinical Study Assessing the Effects of Oral GLP-1 and PYY3-36 Combined with Eligen® Technology on Appetite Suppression

Business Wire: May 26, 2009 – CEDAR KNOLLS, N.J. – Emisphere Technologies, Inc. (NASDAQ: EMIS) has announced data from a clinical study designed to assess the effect of oral administration of two peptides, GLP-1 and PYY3-36, utilizing Emisphere's Eligen® technology, on appetite suppression. The study was conducted at the University Hospital in Basel, Switzerland, by Prof. Christoph Beglinger of the Clinical Research Center, Department of Biomedicine Division of Gastroenterology and Department of Clinical Pharmacology and Toxicology at the hospital.

The randomized, double-blind, placebo-controlled trial was conducted in 16 normal-weight males between the ages of 18 and 40. The study was designed to investigate the effects of orally administered GLP-1 and PYY3-36 formulated with Emisphere's sodium *N*-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) carrier and their potential effect in the control of food intake and satiety. Prior studies have shown the ability of both peptides to reduce appetite and food consumption in healthy subjects and patients with obesity.

The study concluded that these orally administered peptides, when delivered with Emisphere's SNAC carrier, were rapidly absorbed from the gastrointestinal tract, leading to concentrations several times higher than endogenous hormone levels achieved after a standard test meal. Specifically, results showed that oral GLP-1 (2-mg tablet) alone and the combination of oral GLP-1 (2-mg tablet) plus PYY3-36 (1-mg tablet) induced a significant reduction in calorie intake, although there was no synergistic effect when the two peptides were used in combination. Oral PYY3-36 at a 1-mg dose by itself did not significantly reduce calorie intake. Oral GLP-1 (2-mg tablet) and oral PYY3-36 (1-mg tablet) were both shown to induce a rapid increase in plasma GLP-1 and plasma PYY concentrations, respectively.

Prof. Beglinger commented, "This latest set of data incorporating use of Emisphere's Eligen® Technology in oral formulations of GLP-1 and PYY3-36 is very encouraging. Specifically, we see that oral GLP-1, as well as a combination of oral GLP-1 and PYY3-36 was sufficient to affect a meaningful reduction in calorie intake in the study subjects, indicating that further studies in appetite suppression are certainly warranted."

Michael V. Novinski, president and chief executive officer of Emisphere, noted, "This new data represents further evidence of the ability of our Eligen® Technology, and our SNAC carrier, to enhance oral absorption of peptides which normally exhibit low oral bioavailability. In this case, GLP-1 alone and the combination of the two peptides together were able to cross the gastrointestinal tract into the bloodstream in high enough concentrations to significantly affect appetite."

Z-Cube and Yissum Research Development Company Ltd. Sign a Licensing Agreement for the Development of an Innovative Nanotechnology Drug Delivery System for the Treatment of Pain

Business Wire: May 25, 2009 – MILAN, Italy, and JERUSALEM, Israel – Z-Cube Srl, the corporate venture arm of Zambon Company SpA, and Yissum Research Development Company Ltd., the technology transfer company of the Hebrew University of Jerusalem, have announced that they have entered into a licensing agreement for Z-Cube to develop and commercialize an innovative nanotechnology drug delivery system for the treatment of pain. The technology was invented by Professor Elka Touitou of the Department of Pharmaceutics, Faculty of Medicine, Hebrew University of Jerusalem.

Under the terms of the agreement, Z-Cube has received the worldwide exclusive right to develop and commercialize the technology for pain applications and will sponsor a research program to be conducted by Prof. Touitou and her group. Z-Cube has also received the right to grant sublicenses. Yissum will receive license fees, milestones, and royalty payments. "We are pleased to partner with Z-Cube, a world leader in the commercialization of drug delivery technologies," said Yaacov Michlin, CEO of Yissum. "Our novel drug delivery system has the potential to enable relief of both mild and severe pain quickly and efficiently."

The work of Prof. Touitou, a leading authority in the drug delivery field, focuses on the design of novel carriers for enhanced drug absorption and efficiency. Two start-up companies have been established and are active in the development of various novel pharmaceutical products that are based on her previously developed innovative technologies. "This innovative drug delivery system is a powerful tool enabling the development of improved medicines for the treatment of pain," said Lorenzo Pradella, Ph.D., business and operational development director of Z-Cube. "Patients suffering from pain will benefit from this new approach that promises to generate upgraded and easier to use therapeutics."

In 2007, the worldwide market for pain management products (excluding over-the-counter products) was approximately $4.2 billion, representing one of the largest pharmaceutical segments. The expectation is that the demand for prescription pain management products will continue to grow due to favorable demographics, increasing incidence of chronic pain conditions, and heightened awareness of physicians for the need to treat pain. Improved pain treatment includes not only the discovery and marketing of new chemical entities, such as pain killers, but also the development of new delivery systems devoted to reducing side effects, increasing safety, and improving compliance.

RXi Pharmaceuticals Presents Breakthrough RNAi Delivery Technologies at the TIDES® 2009 Conference

Business Wire: May 21, 2009 – WORCESTER, Mass. – RXi Pharmaceuticals Corporation (NASDAQ: RXII), a biopharmaceutical company pursuing the development and commercialization of proprietary therapeutics based on RNA interference (RNAi), has announced that Anastasia Khvorova, Ph.D., the company's chief scientific officer, presented new pre-clinical data on novel RNAi therapeutic approaches at IBC's TIDES® Oligonucleotide and Peptide Technology and Product Development Conference in Las Vegas, NV. This conference is one of the longest-running, most prestigious conferences on oligonucleotide-based therapeutics, a field of drug development that includes RNAi.

Regarded as a revolutionary discovery in biology, RNA interference (RNAi) is a naturally occurring mechanism whereby short, double-stranded RNA molecules interfere with the expression of genes in living cells. RXi's world-leading scientists have made significant advancements in this technology, and Dr. Khvorova presented new forms of potential RNAi drugs with improved therapeutic properties.

Tod Woolf, Ph.D., president and CEO of RXi Pharmaceuticals, commented, "Our research team is making significant progress, and I am very impressed with the amount of robust scientific data generated by our laboratory. The breakthrough technologies presented yesterday by Dr. Khvorova have the potential to address multiple multi-billion dollar therapeutic markets, may lead to improved therapeutics for many currently untreatable diseases and will help RXi realize its goal of becoming the technology leaders in the RNAi therapeutics space."

RXi presented data on the following therapeutically advanced RNAi compounds and delivery technologies:

- **Glucan encapsulated RNAi particles (GeRPS).** The GeRP technology delivers RNAi compounds directly to macrophages. RXi has been building on the work published in an April 30 *Nature* article reporting positive pre-clinical data demonstrating that administration of RNAi therapeutics effectively reduces systemic inflammatory response. RXi has brought the GeRP technology in-house, established manufacturing in its own laboratory, and advanced the technology to the level necessary for further pre-clinical development.
- **Self-delivering RNA (sdRNA).** The proprietary self-delivering-rxRNA™ technology promotes spontaneous cellular uptake of the RNAi therapeutic, which is similar to the uptake of traditional small molecule drugs. Without the use of an additional delivery vehicle, this RNAi delivery technology potentially results in greater efficacy, along with lower costs and fewer side effects attributed to a delivery formulation. RXi believes that self-delivering rxRNA™ should support direct application or subcutaneous administration, opening the door for many clinical areas of RNAi therapeutic development.
- **Advancements to rxRNA™ compounds.** Improvements have been made to rxRNA™ compounds, allowing them to work in concert with the new delivery technologies. Efficient cellular uptake is critical for an effective therapeutic, and advancements have been made to minimize rxRNA™ compounds to improve delivery. These minimized compounds also reduce the immune response and are easier and less costly to manufacture. These advancements are proprietary to RXi and encompass novel and unconventional chemistries compared with current siRNA molecules.

The combination of these new advanced technologies may enable RXi to discover and develop drugs for multiple indications and to build a sustainable pipeline of products for unmet medical needs.

Solvay Pharmaceuticals, Inc. Licenses Exclusive Development and Commercial Rights to Oral Testosterone Formulation from Lipocine Inc.

Business Wire: May 19, 2009 – MARIETTA, Ga. – Solvay Pharmaceuticals, Inc. has announced a licensing agreement with Lipocine Inc. that provides Solvay Pharmaceuticals exclusive rights to develop and commercialize an oral formulation of testosterone. Using its proprietary oral Lip'ral™ technology, Lipocine has developed an investigational oral testosterone product. Solvay Pharmaceuticals plans to initiate a development program to further study the investigational product as an oral treatment for male hypogonadism, also known as low testosterone (low T).

"This agreement further demonstrates Solvay Pharmaceuticals' commitment to men suffering from low testosterone," said

In the News continued on page 34

In the News continued from page 33

Dr. Stephen Hill, president of Solvay Pharmaceuticals, Inc. "As the market leader in the field, we will apply our expertise in the treatment of low testosterone to the development of an oral testosterone replacement therapy. This compound has the potential to be the next major innovation in the management of low testosterone." Dr. Mahesh Patel, president and CEO of Lipocine Inc., stated, "We are quite pleased to partner with Solvay Pharmaceuticals, a leader in testosterone replacement therapy, to bring this innovative treatment option to patients."

Under the terms of the agreement, Solvay Pharmaceuticals will make an upfront payment, make future milestone payments, and pay royalties based on product sales to Lipocine. Solvay Pharmaceuticals will also fund Lipocine development expenses associated with this program.

It is estimated that hypogonadism affects more than 13 million men in the United States age 45 and older. Because signs and symptoms of low testosterone are subtle and often overlap with other common medical conditions, low testosterone is frequently undiagnosed. Signs and symptoms of low testosterone may include low sex drive, erectile dysfunction, fatigue, depressed mood, reduced muscle mass and strength, increased fat body mass, and decreased bone mineral density.

A.P. Pharma Submits New Drug Application for APF530 for Chemotherapy-Induced Nausea and Vomiting

Business Wire: May 18, 2009 – REDWOOD CITY, Calif. – A.P. Pharma, Inc. (Nasdaq: APPA), a specialty pharmaceutical company, has announced that it has submitted a new drug application (NDA) for its lead product, APF530, to the U.S. Food and Drug Administration (FDA). APF530 is being developed for the prevention of chemotherapy-induced nausea and vomiting (CINV) and is a long-acting formulation of granisetron that utilizes the company's proprietary Biochronomer™ drug delivery system. "The submission of this NDA marks a significant milestone for the APF530 program, our Biochronomer™ drug delivery technology and A.P. Pharma as a company," said Ronald J. Prentki, A.P. Pharma president and chief executive officer. "Our number-one priority has been to assemble and submit a complete and high-quality NDA. We thank our regulatory, CMC, clinical and e-filing experts for their tireless efforts and look forward to a timely review by the FDA."

"The favorable efficacy and safety demonstrated in the APF530 Phase 3 clinical program provides a strong foundation for our submission," stated Mr. Prentki. "We believe APF530, which maintains therapeutic drug levels for five days, will be a 'long acting' agent offering important advantages over anti-emetics currently used in the prevention of CINV, and would provide a particular benefit to those many patients suffering with delayed onset nausea and vomiting."

The NDA was submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, whereby the company can rely on the FDA's prior safety and efficacy findings for APF530's active ingredient, granisetron. The FDA is expected to determine whether to accept the NDA for filing within 60 days and to notify the company of its determination within 14 days thereafter. If the NDA is accepted for filing under the Prescription Drug User Fee Act guidelines, it is expected that the FDA will complete its review and provide an action letter with respect to the NDA within 10 months following NDA submission.

Antares Pharma and the Population Council Announce Preliminary Positive Phase II Trial Results

Business Wire: May 15, 2009 – EWING, N.J., and NEW YORK, N.Y. – Antares Pharma, Inc. (NYSE Amex: AIS) and the Population Council have announced preliminary positive results from the Phase II trial for a novel contraceptive gel containing the progestin Nestorone® and the bio-identical estrogen estradiol (NES/E2) utilizing the Antares ATD (advanced transdermal delivery) gel system.

The trial is a dose-finding, open-label, crossover study to evaluate the effect of NES/E2 transdermal gel delivery on ovulation suppression in normal ovulating women. Eighteen women have participated in the trial, which is taking place at three sites (Los Angeles, CA; Santo Domingo, Dominican Republic; and Santiago, Chile) and is scheduled to conclude active treatment in October 2009.

The preliminary data show that all doses suppress ovulation. In addition, no serious adverse events have been recorded, and there have been no instances of skin irritation to date in the study. Each woman in the study receives three separate doses of the gel for 21 days, separated by a washout month in which no products are administered. The primary objective of the study is to find the lowest acceptable dose of the NES/E2 gel to achieve appropriate therapeutic levels for effective contraception (ovulation suppression), as measured by progesterone levels and ultrasound evaluation of follicular development. Secondary objectives include determining the plasma profile of estradiol needed to reach estrogen replacement levels and to maintain regular bleeding patterns. General safety and tolerability of the NES/E2 gel, including any local skin irritation, is also being assessed.

This study follows on the successful completion of a Phase I study, which found an effective combined dose that consistently delivered Nestorone®. In the Phase I study, serum levels following multiple administrations matched the target range expected to provide effective contraception. Blood levels for estradiol were also, on average, within the range for maintenance of a normal estrogenic environment and likely resulting in regular bleeding patterns.

Commenting on the progress of the current study, Regine Sitruk-Ware, executive director for research and development in the Reproductive Health Program of the Population Council, said, "We are encouraged by the preliminary results for this study. This is the first time these formulations have been used with ovulating women, and thus far they are meeting our expectations for both safety and efficacy." Antares Senior Vice President and

Managing Director of the Pharmaceutical Group Dario Carrara, Ph.D., said, "We are very pleased with the progress of the study and that the interim results validate the product concept. A transdermal gel offers an excellent opportunity to provide safe and effective contraception through an innovative drug delivery system in a large and growing global market segment."

The National Survey of Family Growth has revealed that 31% of women discontinue use of reversible contraceptives for method-related reasons within six months of starting use, and 44% do so within 12 months. The novel NES/E2 transdermal gel offers a potentially attractive contraceptive option, in that both the formulation and the active compounds are designed to reduce the adverse events profile observed with current contraceptive methods and, therefore, could result in higher continuation rates by users. Worldwide contraception product sales in 2005 were $3.6 billion, with projections of approximately $4.5 billion by 2010, as reported by Thomson Pharma®.

Under the terms of a joint development agreement, Antares is responsible for research and development activities as they relate to ATD formulation and manufacturing, using the Population Council's patented and other proprietary information covering the compound. The Population Council is responsible for research on Nestorone® and clinical trial design development and management. Together the parties expect to partner Nestorone® with a worldwide or regional organization to commercialize it.

Celsion's Heat-Activated Liposomal Technology Featured in Keynote Address at the International Nanotech and Biotechnology Innovation Conference

Business Wire: May 11, 2009 – COLUMBIA, Md. – Celsion Corporation (NASDAQ: CLSN) has announced that Prof. David Needham, Ph.D., Department of Engineering and Material Science, Duke University, delivered a keynote address entitled "Design and Testing of Novel Thermally Sensitive Liposomal Formulations for Treatment of Local Tumors: A New Paradigm for Drug Delivery" on May 12 at the International Nanotech and Biotechnology Innovation Conference held at the Carlsberg Akademi in Valby, Denmark.

Needham is the inventor of the lysolipid thermally sensitive liposomes (LTSL) technology that Celsion licensed from Duke University. The LTSL technology enables high concentrations of chemotherapeutics to be preferentially deposited in targeted tumors and forms the basis for ThermoDox, which Celsion has advanced into a global Phase III clinical trial to treat hepatocellular carcinoma (HCC or primary liver cancer) and in a Phase II clinical trial to treat recurrent chest wall (RCW) breast cancer.

"Dr. Needham's novel approach to liposome technology has resulted in the development of ThermoDox, a heat-sensitive liposomal formulation of doxorubicin, as the first drug in our product pipeline," stated Michael H. Tardugno, president and chief executive officer. "The LTSL technology is nothing less than ingenious and elegant. We expect that the value of David's invention will ultimately be reflected through the clinical and commercial success of ThermoDox."

"I am pleased to see that my LTSL technology has demonstrated activity that is highly suggestive of clinical benefit in clinical trials. We have seen evidence that the LTSL technology can deliver large concentrations of chemotherapeutics to tumors and it is heartening to realize that a new therapy is on the way to help cancer patients who are battling aggressive end-stage cancers such as primary liver cancer and RCW breast cancer," Needham said.

Lifecore Biomedical Announces Commercial Launch of Corgel™ BioHydrogel Hyaluronan-Based Research Hydrogel

Business Wire: May 11, 2009 – CHASKA, Minn. – Lifecore Biomedical, LLC has announced the commercial launch of its proprietary Corgel™ BioHydrogel research kits. Corgel™ is a hyaluronan (hyaluronic acid)-based biocompatible hydrogel. It was initially conceived and developed by scientists at Cleveland Clinic as a tissue-bulking agent and drug delivery matrix. The tunability of the matrix and its biocompatibility also allow for direct inclusion of cells or bioactive agents.

Lifecore procured an exclusive license agreement with Cleveland Clinic in 2007 and has been actively developing the technology by completing ISO 10993 safety and toxicity studies, as well as exploring modifications and variables to the technology. Lifecore now looks forward to collaborative development for use in surgical and transcatheter applications in vascular surgery, cardiology, ophthalmology, orthopedics, aesthetics, ENT, drug delivery, tissue engineering, and regenerative medicine and several other medical fields.

Teikoku Pharma USA Acquires Travanti Pharma Inc.

Business Wire: May 8, 2009 – SAN JOSE, Calif. – Teikoku Pharma USA Inc., an international specialty pharmaceutical company, has announced that it has acquired, effective May 8, 2009, Minneapolis area-based Travanti Pharma Inc., a privately held corporation that designs, develops, and markets innovative drug delivery platforms that improve the safety, compliance, effectiveness, and ease of administration of medications delivered to the body.

The company has developed a proprietary wearable electronic disposable drug delivery technology (WEDD®) platform. WEDD® is an innovative electronic transdermal (iontophoretic) drug delivery system that is totally self-contained, single-use, portable, and disposable. The company has a number of ready-to-partner clinical projects focused on improving the delivery of therapeutic medications. The acquisition is part of Teikoku's core strategy to develop transdermal pharmaceutical products by applying drug delivery technology to make administration of medicines safer and/or more effective, more controllable, and, in some cases, eliminating the need for injection.

In the News continued on page 36

In the News continued from page 35

"The acquisition of Travanti Pharma broadens Teikoku's transdermal delivery capabilities and enhances Teikoku pipelines in the areas of pain and CNS," said Masahisa Kitagawa, president and CEO. "We are very pleased to join forces with Teikoku, a company that understands our business well and has the capabilities to help move several excellent products based upon Travanti's WEDD technology into the marketplace," commented Robert Cohen, president and CEO of Travanti Pharma. "It is gratifying to complete a transaction that benefits Teikoku, as well as Travanti's shareholders and employees."

InCube Labs Adds Pharmaceutical Expertise, Creates Drug Delivery Group

Business Wire: May 5, 2009 – SAN JOSE, Calif. – InCube Labs, one of America's most successful medical innovation centers, has announced it has broadened its focus to include pharmaceuticals and cell biology and created an interdisciplinary team focused on tissue engineering and innovative drug delivery platforms. The company has added deep pharmaceutical expertise to support this aggressive research agenda, most notably with the addition of M. Hashim, R&D expert and former head of the Pharmacology Section at GlaxoSmithKline. Joining Hashim to drive InCube's development of groundbreaking drug delivery methods is clinical development expert Sanjay Patel. The tissue engineering team welcomes Emily Arnsdorf (previously at Stanford University), biophysicist Lu Wang, and micro-scale manufacturing design expert Paren Shah.

"Other companies have dabbled in cross-functional research, but InCube is the first company to pursue drug-device combinations with a team equally expert in drugs and devices," said Mir Imran, founder and CEO of InCube. "Too much of today's research is focused on trying to adapt existing technologies and therapies to tackle new clinical problems; at InCube, we are creating innovative platforms to address specific medical challenges. The best way to do this is with an interdisciplinary team; and the breadth and depth of expertise that we now have under one roof is unprecedented."

Founded by Imran in 1995, InCube has a successful track record that includes groundbreaking innovations and 14 successful medical device companies. One of America's most prolific medical innovators and inventors, Imran has more than 200 patents and more than 20 successful companies to his name, and he is best known for the invention of the first implantable cardiac defibrillator.

InCube is now applying its trademark approach of fostering groundbreaking innovation in medical devices to novel site-specific drug delivery platforms and tissue engineering. With the addition of Hashim, Patel, Wang, Arnsdorf, and Shah, along with Imran's own multi-disciplinary background, InCube is creating a true merger of device and drug expertise. The revolutionary approach overcomes chronic deficiencies that have long plagued traditional pharmaceutical and device companies. Unlike other companies that develop new technologies and then seek to apply them to a problem, InCube's research and innovation is driven by clinical needs. InCube's drug-device combination team is already tackling such ills as migraine, atrial fibrillation, epilepsy, anemia, diabetes, obesity, renal disease, depression, anxiety, and Alzheimer's disease with an array of novel drug delivery platforms and drug formulations, including intrapulmonary, transdermal, intranasal, gastrointestinal, and intramuscular. In addition to pharmaceuticals delivery, the group will focus on the delivery of biotherapeutics, including proteins, peptides, and vaccines.

The group is led by Hashim, a scientist and R&D expert who has been involved in the discovery and development of numerous drugs in a variety of therapeutic areas, including CNS, cardiovascular, anesthesia, cancer, diabetes, and obesity. Most recently, he served as the head of the Pharmacology Section within the Division of Biology/Metabolic Diseases at GlaxoSmithKline, where he was responsible for both the organization and management of the section. Hashim brings extensive experience in physiology, pharmacology, and drug discovery and development to InCube. He has authored numerous peer-reviewed journal articles, patents, scientific briefs, and expert reports for regulatory submissions.

"After more than twenty years in the industry, I know firsthand that big pharma is starting to exhaust the number of blockbusters it can create using the same old methods," said Hashim. "Drugs fail today not because they are ineffective, but because they have harmful side effects. The next wave of pharmaceutical innovation is as much about new molecules as about how they are delivered. We're combining expertise in drug development, biology, engineering and material science to approach medical treatments in a new way that maximizes efficacy and minimizes side effects."

Hashim is joined by Sanjay Patel, a pharmaceutical industry veteran with 20 years experience. He has contributed to numerous clinical development programs of FDA-approved drugs across several therapeutic areas, including anesthesia, multiple sclerosis, chronic intractable pain, Crohn's disease, diabetes, and arthritis. Patel has led clinical development teams at several small- and medium-sized public pharmaceutical companies.

InCube's tissue engineering team is led by Arnsdorf, a scientist with a Ph.D. in bioengineering and expertise in stem cell biology and regenerative medicine. She is joined by Wang, a biophysicist and a Ph.D. in physiology and neurobiology, and Shah, who brings 20 years of engineering experience in robotics, lasers, and biomedical device design.

APRIL 2009

Lilly and Amylin Team Up to Create Diabetes Pen

in-pharmatechnologist.com: April 30, 2009 – Eli Lilly and Amylin Pharmaceuticals are jointly developing an exenatide once-weekly pen device that should provide a more convenient way for diabetics to treat themselves. The pharma industry has been striving to improve diabetic care by creating alternative drug delivery systems that will increase compliance and alleviate

the need for daily injections. Weekly administration using a pen device would mark a significant advance in the convenience of diabetes treatment and put the companies in a strong position in a lucrative market.

Lilly and Amylin were already working on a once-weekly formulation of exenatide, but following a patient survey opted to create a drug delivery device to improve the product. Vince Mihalik, senior vice president of sales and marketing and chief commercial officer at Amylin, said, "The agreement for an exenatide once weekly pen device underscores our commitment to enhance the user experience for patients with type 2 diabetes. "While our DURATION-1 patient questionnaire results showed that the delivery system used in clinical trials was well accepted by patients, we continue to look for ways to enhance delivery and offer patients a range of choices through alternative delivery possibilities."

The pen will have pre-filled dual chambers that allow the patient to mix and administer the exenatide and will replace the vials and syringes previously used in Phase I and II trials.

Nanoparticles Used to Create Topical Viagra® Rival

in-pharmatechnologist.com: April 29, 2009 – Erectile dysfunction could be treated by a nanoparticle formulation applied directly to the penis, according to research, reducing the side effects that can occur when taking drugs like Viagra®.

People taking erectile dysfunction (ED) medications such as Viagra® (sildenafil citrate) and Cialis® (tadalafil) can experience side effects, including headaches, facial flushing, and indigestion. Research presented at the 104th Annual Scientific Meeting of the American Urological Association (AUA) suggests that topical application of a nanoparticle formulation could be effective and reduce side effects. The formulation consists of a hydrogel and glass nanoparticle platform that is capable of sustained release of nitric oxide (NO), a compound that can aid ED by relaxing smooth muscle cells and expanding blood vessels so they fill with blood.

Currently the treatment is in preclinical testing but has shown effectiveness in rats. The drug delivery formulation could also be applied to other ailments that would benefit from topical administration. Ira Sharlip, an AUA spokesman, said, "This is a very interesting concept which has potential to impact treatment of many conditions including erectile dysfunction if it can be translated from the animal lab to clinical practice. It remains to be seen whether the effect of the nanoparticle technology is a local or a systemic effect."

The researchers investigated the effectiveness of the formulation by applying it to the penis skin of seven rats and measuring the erectile response by intracorporal pressure/blood pressure (ICP/BP) ratio. Of the seven rats that had the formulation applied, five experienced a positive change in the ICP/BP ratio and had visible erections. The average time for erectile response was 65 minutes.

The 2005 market for ED drugs was valued at $1.95 billion by Datamonitor, and this is predicted to grow because of the aging population, rising obesity, and lessening of the social taboo. This represents a sizeable market for companies such as Pfizer and Eli Lilly, and extending the life-cycle of their products will increasingly become a priority when generic competition approaches. Consequently, alternative drug delivery technologies that can provide benefits such as lower doses and reduced side effects could become increasingly attractive in the coming years.

Patheon to Make Oros®-Based Depression and Allergy Drugs

in-pharmatechnologist.com: April 28, 2009 – Canada's Patheon has been contracted to commercialize treatments for allergy and depression using the Oros® controlled release technology at its manufacturing facility in Cincinnati, OH. The Oros® technology was originally developed by U.S. pharmaceutical firm Alza, now part of Johnson & Johnson (J&J), as a way of gradually releasing active pharmaceutical ingredients (API) over an extended period.

Terry Novak, Patheon's president of North American operations, said, "Patheon has developed the expertise for the Oros technology in collaboration with clients and the equipment manufacturer and developed the Cincinnati facility as the Center of Excellence for controlled release technologies." Novak added, "The development and manufacture of Oros® technology products is highly involved and challenging compared to other conventional dosage forms," explaining that considerable technical expertise is needed to produce any osmotic drug delivery technology. He went on to say that the Cincinnati plant's solvent-capable coating pans, humidity-controlled tray dryers, bi-layer tablet presses, laser drills, fluid bed granulators, and dissolution testing capabilities made the project possible.

The first drug is expected to launch in the United States later this year, with the second expected to reach the market in 2010.

Trial of Nanoparticle-Delivered Anti-cancer Gene Progresses

in-pharmatechnologist.com: April 23, 2009 – Research has been presented on the first Phase I trials of a systemic, non-viral, targeted nanoparticle that delivers a p53 tumor suppressor gene to combat cancer. The nanoparticle has been designed to locate primary and hidden metastatic tumors and deliver the suppressor gene, which is known to play a key role in the pathogenesis of tumors.

Developments in the trial were presented at an American Association of Anatomists (AAA) scientific session by Esther Chang, who developed the nanoparticle with colleagues at Georgetown University Medical Center's Lombardi Cancer Center. The nanoparticle is essentially a fat droplet that envelops the p53 suppressor gene, with a tumor-targeting antibody attached. Once the nanoparticle has reached a tumor, the gene is delivered, and the fat droplet biodegrades.

In the News continued on page 38

In the News continued from page 37

Currently there are 6 patients with a variety of cancers enrolled in the trial, but this number is expected to rise to 14. Chang reported that early results from the trial are promising, with anti-tumor efficacy being demonstrated and safety data accumulated.

Extensive research has been undertaken into the role p53 plays in the formation of tumors, which has been built on by preclinical trials investigating the effectiveness of the suppressor gene. Chang's research group used animal models to test the effectiveness of p53 against 16 different types of tumor, including prostate, pancreatic, melanoma, and breast and head and neck cancers. The gene was used in conjunction with conventional cancer therapy and "dramatically improved the efficacy." By improving the effectiveness of the treatment, the researchers believe that lower doses could be administered, which would reduce side effects.

Normally functioning cells have two copies of the p53 gene, which produces a protein that can coordinate cell repair or induce cell death. When p53 stops functioning normally, malignant cell growth can occur, and the gene's malfunction has also been linked to the resistance of some tumors to chemotherapy and radiotherapy.

IntelGenx Furthers Novel Antihypertensive Formulation

in-pharmatechnologist.com: April 22, 2009 – IntelGenx' clinical pilot study indicates the bioequivalence of a leading antihypertensive and its product, which has been developed using its multilayer Versatab delivery technology. Versatab is a multilayered tablet that can contain up to three active pharmaceutical ingredients (APIs), eliminate non-linear delivery profiles, and improve compliance by reducing tablet intake. IntelGenx is now beginning scale up and manufacture of the product, called INT001. The pivotal bioequivalence study is anticipated to take place in Q3, with an abbreviated new drug application (ANDA) filed in Q4.

Horst Zerbe, president and CEO of IntelGenx, said, "Once again our scientists, our technology and our expertise have proven to be successful. We were confident going into this clinical study and we are delighted with these results. This is a significant achievement for IntelGenx that reaffirms our technological capabilities. We are now eager to move forward to the next level of pivotal clinical studies with our partner DAVA Pharmaceuticals."

The product is the result of a partnership between IntelGenx and DAVA that the companies entered into in March 2008. Under the terms of the agreement, IntelGenx is developing the product, and DAVA will be responsible for U.S. commercialization and marketing activities.

INT001 has been developed using IntelGenx' Versatab drug delivery formulation, which the company developed to improve on existing controlled release tablets. IntelGenx claims that its tablets can be formulated to have a linear delivery profile, unlike single-layer tablets, because the API can be sandwiched between two excipient layers that erode over time.

Zealand Licenses Vyteris' Transdermal Patch

in-pharmatechnologist.com: April 16, 2009 – The drive to license needle-free delivery methods continues with Zealand Pharma signing a deal to use its peptide optimization technology with Vyteris' controlled transdermal patch. Needle-free delivery has been identified by pharma as a more convenient route of administration that could increase patient compliance and extend a product's lifespan. Zealand is the latest company to license a needle-free technology, opting to use Vyteris' smart patch in preclinical develop of one of its peptide drug candidates.

Haro Hartounian, president and CEO of Vyteris, said, "Needle-free, tightly controlled delivery of peptides via active, transdermal patches is an innovative and patient-friendly route of administration which can lead to increased safety and compliance. Our ongoing female infertility project with Ferring Pharmaceuticals has now entered clinical Phase II, and we hope to continue this success in transdermal peptide delivery with our new partner Zealand Pharma." After Zealand's preclinical trial is completed, the companies have the option to continue the development of the formulation or begin work on other drug candidates.

Vyteris claims its smart patch system offers advantages over current techniques in numerous fields, including cardiovascular, diabetes, and pain management. When a positive charge is applied to the patch's therapeutic-holding reservoir, the drug is released and can pass through the skin. This is possible because many drugs are positively charged and, therefore, are repelled by electrical stimulation, which forces them out of the reservoir and through the skin. By varying the strength of the electrical charge, it is possible to administer the therapeutic to different depths, with stronger stimulation delivering the drug to the circulatory system and a weaker pulse providing topical treatment. In addition, the timing of therapeutic release can be controlled, allowing the patch to mimic an injection, timed interval release, and sustained delivery, with the option for a spike in dosage if required.

Phylogica Targets Intranasal Peptide Delivery

in-pharmatechnologist.com: April 14, 2009 – Phylogica is developing formulations of its Phylomer peptides using Aegis Therapeutics' Intravail absorption enhancers, which enable transmucosal drug delivery. Aegis claims that the excipients present in Intravail increase intranasal bioavailability to levels comparable to subcutaneous injection, making it an effective, more convenient alternative. Phylogica is using this technology to further develop its Phylomer peptides, which it believes are the ideal size for nasal delivery and will benefit from the advantages offered by Intravail.

Ed Maggio, CEO of Aegis, said, "Intranasal delivery is the most validated non-injectable means of delivering peptides since several peptides including calcitonin, desmopressin, and nafarelin have been approved and marketed for years. Intranasal

formulations have been shown to increase market share by more than 30 fold over the corresponding injectable formulations, because patients overwhelmingly prefer to avoid injections if possible in favour of other delivery approaches."

The companies will offer their combined services to pharmas that are looking to develop intranasal peptide formulations against a specific target. Aegis and Phylogica's collaboration will utilize their respective proprietary technologies, which both claim offer significant advantages compared with competitors. Intravail consists of transmucosal absorption enhancement agents that are "safe, odourless, tasteless, non-toxic, non-irritating, non-denaturing, and non-mutagenic" and metabolized to CO_2 and H_2O after delivery.

The technology is capable of delivering therapeutics up to 30,000 Da and can be used for administration routes other than intranasal, such as ocular, pulmonary, and transdermal, according to Aegis. In addition, Intravail is compatible with standard, off-the-shelf nasal delivery systems, and consequently, clients do not have to invest in special manufacturing equipment. This will now be used to deliver therapeutics taken from Phylogica's Phylomer peptides, which the company claims are quicker to manufacture and easier to deliver than antibodies.

POM Formulation Offers pH-Responsive Targeted Colon Delivery

in-pharmatechnologist.com: April 9, 2009 – Researchers have developed a pH-responsive formulation that could be used to deliver a polyoxometalate (POM), which has broad spectrum anticancer and antiviral properties, to the colon. POMs are metal–oxygen cluster compounds that are cheaper and easier to synthesize than small molecules. Despite these benefits, and the effectiveness of POMs against an array of ailments, including HIV and lung cancer, difficulties in stabilizing the compounds and delivering them to specific regions has restricted usage.

However, research published in *Dalton Transactions* suggests that attaching a POM to mesoporous silica spheres with a dative bond creates a stable formulation that could be used for drug delivery. The dative bond is unaffected by acidic or neutral conditions, which would be experienced during oral drug transit through the body, and the POM remains attached to the silica spheres. However, when put in a basic environment, such as the one found in the colon, the dative bond breaks, and the POM is released. This pH-responsive release has led the researchers to speculate that the technique could be used in the treatment of colon cancer. Others have attempted to use the change in pH as a trigger for targeted release, such as Cosmo Pharmaceuticals, which filed a patent for its MMX technology.

The researchers believe their technique could be used to deliver various drugs containing transition metal. These include compounds already in clinical use, such as cisplatin, carboplatin, and oxaliplatin, which may be more effective than the POM used by the researchers, which only "showed modest antitumoural activity."

Researchers Shed Light on MRSA Treatment

in-pharmatechnologist.com: April 7, 2009 – Methicillin-resistant *Staphylococcus aureus* (MRSA) could be treated through a combination of an antimicrobial drug, a peptide, and light, according to researchers who have hailed the treatment as a "magic bullet." The treatment has yet to enter clinical trials, but the profile of MRSA, which has been raised by media furor over its presence in hospitals, means that the positive laboratory results have been eagerly received.

Despite the levels of interest in MRSA, its resistance to an array of antibiotics has hindered development of a treatment, but researchers now believe they may have found a novel way of helping patients. The researchers attached an antimicrobial agent, tin chlorin e6 (SnCe6), to a peptide that targets and binds to MRSA. Targeting the formulation with light, the wavelength of which has not been published, results in the production of free radicals and an unstable form of oxygen that damages and kills bacteria.

Linda Dekker of University College London, said, "The results from laboratory studies are very encouraging and indicate that this technique might be effective at treating topical infections such as wound and burn infections. This work will require *in vivo* trials before it can be used. Due to the growing resistance of many organisms to antibiotics, this approach may be the only one available for use against microbes resistant to all known antibiotics."

In the laboratory tests, 99.97% of 10m MRSA cells were killed, which the researchers claim is 1,000 times more effective than treatment with tin chlorin e6 alone. Furthermore, the new treatment should result in less damage to human cells, and MRSA is very unlikely to develop resistance to it, according to the researchers.

The MRSA treatment was publicized a few days after a special issue of *Photochemistry and Photobiology* that examined the increasing prominence of light-activated drug delivery systems. Researchers have seen promise in the use of light in the UV, visible, and near-infrared range to activate materials sensitive to innocuous electromagnetic radiation. As well as single-use delivery systems, which the MRSA treatment is an example of, researchers have also been working on materials capable of undergoing reversible structural changes, which would release a therapeutic in pulses in response to cycles of light and dark.

Altea Inks Deal to Use Byetta™ with PassPort® Patch

in-pharmatechnologist.com: April 2, 2009 – The search for more convenient diabetes treatments continues, with Altea Therapeutics reaching a $46 million agreement with Eli Lilly and Amylin to develop a transdermal patch administering Byetta™. Use of Altea's PassPort® patch technology is intended to provide a viable alternative to injections, which the company believes could potentially improve patient compliance. Altea has already completed a Phase I trial of the therapeutic and will now

In the News continued on page 40

In the News continued from page 39

continue its development, with Lilly and Amylin funding this as well as the product's manufacturing and commercialization costs. Eric Tomlinson, CEO of Altea, said, "We believe the diabetes care experience of Lilly and Amylin, combined with the transdermal expertise of Altea Therapeutics creates an excellent partnership for the potential development of the world's first transdermal GLP-1 receptor agonist, transdermal exenatide (Byetta™)."

Altea may receive up to $46 million (€34.7 million) from Lilly and Amylin, composed of an upfront license payment and clinical, regulatory, and sales milestones. Altea will also receive royalties on product sales, and Lilly and Amylin have made an undisclosed equity investment in the company.

PassPort® consists of a disposable patch and a reusable handheld applicator that is capable of delivering therapeutics through the surface of the skin that normally have to be injected. This is achieved using an electrical pulse to create microchannels through which the therapeutic, such as a water-soluble protein or carbohydrate, can pass. By applying this technology to the type 2 diabetes market, Altea believes it can meet the demand for more convenient forms of drug administration. This demand has also led to Lilly and Amylin developing a once-weekly formulation that would save patients from having to administer daily injections. Steven Damon, senior vice president, business development at Altea said that he was aware of this formulation but believed that his company's "once a day transdermal exenatide will meet an unmet need in the marketplace." In addition, although Byetta™ has been linked to deaths that led to the U.S. Food and Drug Administration (FDA) moving to strengthen the warning label, Damon believes the safety of Altea's patch "will be established in clinical studies."

Damon outlined the other products being developed with PassPort®, which include formulations Altea is taking through preclinical trials in conjunction with several pharmaceutical companies. Damon also said, "We are developing a once a day transdermal basal insulin product, also in Phase I clinical development. Additionally, we are developing what we hope to be a daily fentanyl citrate patch, in Phase I clinical development, which may greatly increase the safety and efficacy of marketed fentanyl patches."

MARCH 2009

FluGen Vaccine Delivery Micro-device

in-pharmatechnologist.com: March 31, 2009 – FluGen has secured the exclusive rights to Ratio's novel vaccine delivery technology, which is a disposable micro-device that it claims can improve efficacy and compliance. The benefits of the device are claimed to be most pronounced among users who are over the age of 65, who are also more at risk from influenza, with efficacy increasing most among this group and the easy, pain-free delivery hoped to improve vaccination rates. FluGen will now begin preclinical testing of the device using its cell-based trivalent influenza vaccines (TIVs), with the company hoping to submit an investigational new drug (IND) application to the U.S. Food and Drug Administration (FDA) in the second half of 2010.

Paul Radspinner, president and CEO of FluGen, said, "This exciting vaccine-delivery technology from Ratio is an important expansion of FluGen's product pipeline. It will allow the company to offer the $6bn (€4.5bn) influenza vaccine market not only superior vaccines, but an easy-to-use, painless delivery technology that increases vaccine effectiveness. FluGen looks forward to advancing this valuable product through our pipeline with one or more TIVs."

The micro-device is similar in size to a poker chip and contains a miniature fluidic pump that is activated at the press of a button. This sends the vaccine from its reservoir, through a set of microneedles and delivers it intradermally or into the skin. Unlike traditional delivery techniques, the vaccine is not delivered into the muscle, and FluGen believes this has the potential to increase the treatment's efficacy, which it claims can be as low as 20% with syringe delivery in some patients. ■

Erratum

CRS Newsletter
Volume 26, Number 2, 2009

In the Scientifically Speaking article "Enhancing the Intracellular Release of siRNA with Biodegradable Poly(ethylene imine) as a Carrier System" by Breunig et al. (pages 4–5), the correct spelling of the second author's name is Constantin Hozsa. In addition, the correct page range for the paper cited in footnote 1 on page 4 is 57-63.

Look to the Future with CRS!

Development and Regulatory Challenges for Controlled Release Formulations

Co-sponsored by the American Association of Pharmaceutical Scientists (AAPS)
Being Held in Conjunction with the AAPS Annual Meeting

November 7-8, 2009
Los Angeles Convention Center
Los Angeles, CA U.S.A.

37th Annual Meeting & Exposition of CRS

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

38th Annual Meeting & Exposition of CRS

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

39th Annual Meeting & Exposition of CRS

July 14-18, 2012
Centre des Congrés de Québec
Québec City, Canada

CRS
Delivering Bioactives

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

Calendar of Events

2009

Advances in Tissue Engineering
August 12-15
Rice University
Houston, Texas, U.S.A.
www.ruf.rice.edu/~mikosgrp/pages/ATE/ate.htm

SFI Irish Drug Delivery Network (IDDN) Cluster Conference (with UKICRS)
August 19
University College Dublin
Dublin, Ireland
www.ucd.ie/iddn/

4th International Pharmaceutical Symposium
September 24-26
Fudan University Zhangjiang Campus
Shanghai, China
www.dds-china.org/

EuroNanoMedicine 2009
September 28-30
Bled, Slovenia
http://events.dechema.de/euronanomedicine2009

Development and Regulatory Challenges for Controlled Release Formulations Joint Workshop in conjunction with AAPS
November 7-8
Los Angeles Convention Center
Los Angeles, California, U.S.A.
www.controlledreleasesociety.org/main/meetings/

2009 AAPS Annual Meeting and Exposition
November 8-12
Los Angeles Convention Center
Los Angeles, California, U.S.A.
www.aapspharmaceutica.com/

2010

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

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