CRS Leading Delivery Science and Technology

Newsletter

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Leading Delivery Science and Technology

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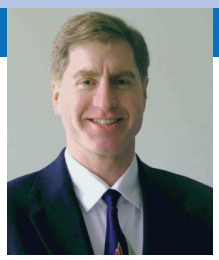

Steven Giannos
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Changes

In this issue of the *CRS Newsletter*, there is a wonderful interview with Vincent H. L. Lee in which he discusses the magic of change. Dr. Lee, past president of the Controlled Release Society, talks openly about having early onset Parkinson's disease and the many changes, professionally and personally, he has gone through. He also discusses what it's like to be on both sides as a scientist and as a patient.

I am struck by his story, seeing as I have relatives with Parkinson's disease and Alzheimer's disease and can readily identify with the challenges that the individual as well as the caregiver must face. As an example, a presentation given by a clinician at a patient-centered drug delivery workshop I attended a couple of years ago showed one slide that brought the issue home. The slide showed a bowl of applesauce. The presenter went on to say that we put so much care into developing the controlled release formulation, but ultimately it may wind up ground to a powder and mixed with applesauce for patients with difficulty in swallowing.

This is what makes continual research and product development important. We don't just sit back complacently and say that's the best we can do. We are constantly looking ahead for the best way to treat the individual and ensure ease and patient compliance. Wearables and the Internet of everything are on the horizon, as well as nanotechnologies and monoclonal antibodies and antibody-drug conjugates for targeted drug delivery. Dr. Lee touches on some of these technologies and future developments for controlled release as well as his professional career and advice for young scientists.

Also in this issue is a Scientifically Speaking article on ocular drug delivery. The article is a good overview of ocular delivery and recent developments in ocular technologies. Did you know that there is a CRS Ocular Delivery LinkedIn Group?

Something to look forward to for attendees of the 2015 CRS Annual Meeting in Edinburgh, Scotland, this coming July is "Introduction to Microencapsulation," a workshop that draws a large and diversified audience. Technology experts will provide an introduction to state-of-the-art microencapsulation techniques used throughout multiple industries for controlled release applications, followed by lab-scale demonstration of many of the discussed processes. Additionally, Roger H. Pak, chair of the Therapeutic Bioconjugate Workshop, discusses "Delivery of Therapeutic Bioconjugates: From Polymer Conjugates to Antibody-Drug Conjugates."

Also inside is a report from the 7th Annual CRS Italy Chapter workshop on "Drug Delivery Systems: Pharmacokinetic Challenges and Targeting Strategies," as well as an update of articles from the Preclinical Sciences & Animal Health Division and the In the News section.

Enjoy the newsletter and keep moving forward.

Best regards,
Steven Giannos ■

Art Tipton
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Volunteering and Giving Back

It has been a fruitful time for CRS. The Board and many other volunteers have been diligently working on behalf of CRS, and I want to provide an update for a few of them with a focus on the annual meeting strategy and program, the science agenda of CRS, the journals, and the newsletter. These efforts ensure we remain the best and most relevant society in our field.

As many of you already know, the CRS publication *Drug Delivery and Translational Research* (*DDTR*) has been accepted for indexing in PubMed. This is an important milestone for the journal. Applications are reviewed by the National Library of Medicine for indexing in PubMed. The decision is based on stringent criteria including timely publication of issues, quality of papers published, value of the journal, credentials of the editorial team, and ethical compliance. Given the competition and the high hurdle, the success rate is low: it was only 12% in 2014. *DDTR* made it on the first attempt—and so a hearty thank you for all the efforts to editor-in-chief **Vinod Labhasetwar** and all the team associated with *DDTR*.

The *Journal of Controlled Release* continues to excel, and the impact factor has grown from 5.73 in 2011 to 7.26 today thanks to the efforts of editor-in-chief **Kinam Park** and a sterling editorial board.

You may read this commentary on the CRS homepage, but it is initially prepared for the *CRS Newsletter* and is included there. I do the very light lifting of writing a short piece a few times a year for the *CRS Newsletter*. The Newsletter Committee under the leadership of **Yvonne Pierre** does the yeoman's job of preparing this stellar newsletter. Always a quality product, several members have commented to me that it is even getting better.

For our upcoming annual meeting in Edinburgh, our Annual Meeting Program Committee has been working on a number of deadlines recently. **Justin Hanes** recently led the committee through a final process to slot all the abstracts for the best possible annual meeting. As president I have been fortunate to be working with Justin and his dedicated team, since a priority this year was to redesign the 2015 annual meeting. As just one example, you are used to having three excellent plenary sessions. Edinburgh will have those—and then on top will have two additional special sessions with talks by Vincent H. L. Lee and Nicholas A. Peppas. Imagine the most rewarding scientific CRS meeting you have enjoyed, and layer on top of that talks from two luminaries and past CRS presidents such as Vincent and Nicholas! You will have a great scientific meeting in Edinburgh, and we are also working diligently on creating an outstanding social and networking experience. You will receive regular notices over the next several weeks, but be sure to read about our special event at the **Assembly Rooms, a UNESCO World Heritage Site** that you will not want to miss!

While planning a meeting for this year is hard, imagine working to design a meeting five years from now! That is what **Christian Seiler** and the Annual Meeting Committee are tasked with by the Board. As this group looks and tries to clear the "fog of the future" to what annual meetings will look like in 2020, they provide input useful to the Annual Meeting Program Committee and also are starting to put together a roadmap for how to make our annual meeting increasingly relevant.

In previous commentaries I have covered two of our energetic committees: the Young Scientist Committee under the leadership of **Patrick Lim Soo** and the C&DP Division with its chair, **Chris McDaniel**.

These are just a few of the many committees and volunteers who work for CRS. Here is a link to all the committees and volunteers: www.controlledreleasesociety.org/community/Pages/CRSCommittees.aspx

Many years ago in the United States, President John F. Kennedy famously said in his inauguration speech, "ask not what your country can do for you, ask what you can do for your country." I think of that quote often and am so thrilled to work alongside so many volunteers who think that way on behalf of CRS—people who give tirelessly of their time, often donate money, and do so with a passion. As only one small part of that band of volunteers and donors, I do so because CRS was so important in my career, and I would feel amiss if I did not give back. I am continually inspired that so many of you continue the ongoing legacy of CRS and our founders. On behalf of the members and Board, thank you.

Art Tipton ■

The Magic of Change: A Conversation with Vincent H. L. Lee

Vishwas Rai[1] and Bozena B. Michniak-Kohn[2]

"This interview is about change: what does it mean for me personally and professionally; what are the changes in science, technology, and society driving the transformation of drug discovery and development; and what role can Asia play in the transformation," remarked Vincent H. L. Lee, research professor and former director (2006–2014) of the School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong. In his 35+ year long career, Dr. Lee has left his footprints in the academic, industrial, and regulatory worlds of drug development across two continents (North America and Asia). Such a career progression was not planned but was influenced by the diagnosis of his Parkinson's disease (PD) in December 1999.

Dr. Lee left Hong Kong for the United States at the age of 16 to study medicine by way of pharmacy. It was in pharmacy school that he had his first encounter with research. Although it was not love at first sight, he could not resist the euphoria of a successful scientific inquiry. As a result, he decided to attend graduate school instead of medical school. In 1975, he was awarded a WARF Fellowship from the University of Wisconsin, where he earned his M.S. and Ph.D. degrees.

He began his professional career at the University of Southern California (USC) as an assistant professor in 1979 and continued to become a distinguished professor, chairman of the Department of Pharmaceutical Sciences, and associate dean for research and graduate affairs. He joined ALZA for a brief period of time as vice president of formulation, biological, and material sciences before becoming an associate director of the Office of Pharmaceutical Science, Center of Drug Evaluation and Research at the Food and Drug Administration (FDA).

Dr. Lee freely volunteered his time to benefit the pharmaceutical sciences community. He was elected president of the Controlled Release Society in 1993 and of the American Association of Pharmaceutical Scientists (AAPS) in 1996. In 1993, he became co-founding editor of the *Journal of Drug Targeting* at the invitation of Sandy Florence, then the dean at the University of London School of Pharmacy. Before long, his editorial talent was sought after by the publishers of *Advanced Drug Delivery Reviews* (*ADDR*) and *Pharmaceutical Research*. Under his decade-long editorship, the impact factor for *ADDR* was increased sevenfold, and that for *Pharmaceutical Research* was doubled. In addition to his editorial duties, he is a reviewer for numerous international high-impact journals.

He enjoyed writing research proposals and was successful 80% of the time on first submission in securing research funding from both public and private organizations from all over the world, including the National Institutes of Health (NIH), United States Pharmacopoeia, American Diabetic Association, Allergan Corporation, Lilly Research, Bausch and Lomb, Carlbiotech, Hisamitsu, and Sandoz. He is internationally known for his research in ocular drug delivery and peptide and protein drug delivery. His current research interests include precision medicine and accelerated drug development.

Several international honors and awards have recognized his research excellence. They include the CRS Young Investigator Award, AAPS Research Achievement Award in Pharmaceutics and Drug Delivery, Nagai Distinguished Pharmaceutical Scientist Award of the Federation of Asian Pharmaceutical Association, Pharmaceutical Scientist of the Year award of the FIP Board of Pharmaceutical Sciences, and Citation of Merit by the University of Wisconsin School of Pharmacy. In 2003, he was awarded an honorary doctor of science degree from the University of London, United Kingdom.

Dr. Lee is presenting one of the four plenary sessions at the upcoming CRS Annual Meeting. There, he will share how his personal struggle with PD and his tenure at ALZA and subsequently at the FDA have sharpened his appreciation for the sea change in the culture of drug delivery science and regulation that must take place for society to benefit from the promise of customized drug delivery in a timely manner.

Q *How would you describe your career path?*

A A fascinating journey with memorable twists and turns. At the age of 48 when I was diagnosed with PD, I knew my dream of leading a major research university someday was unrealistic. Over time, I found myself increasingly withdrawn from public events. I was overly conscious of my clumsiness and was terrified by the thought of accidentally falling off the stage after giving a speech or ending a talk.

Four years ago, I began experiencing the textbook description of reduced effectiveness of levodopa on prolonged use, so I found it necessary to alter my dosing regimen in hopes of minimizing the frequency as well as duration of frozen gait episodes. Nevertheless, I was unable to predict which dose would work and for how long.

Although three extended release formulations of carbidopa and levodopa for advanced PD were making their way through regulatory review (in 2014), none was anywhere near approval at the time when I needed a proven therapeutic solution. I reached the point where I considered myself a burden to my students and colleagues because of the constellation of symptoms that interfered with my

1 Chrono Therapeutics Inc., Hayward, CA, U.S.A.
2 Ernest Mario School of Pharmacy, Rutgers–The State University of New Jersey, U.S.A.

effectiveness. On July 31, 2014, I underwent a 10 hour deep brain stimulation surgery, for 8 hours of which I was awake but sedated. The operation was a success.

Q *How may a Ph.D. with aspirations for academia prepare himself or herself for success?*

A There are three interrelated elements: research leadership, research collaboration, and advocacy by mentors.

No matter where you are, promotion in academia uses the same yardstick, namely, your leadership in a research area you developed. I have seen research careers flourish because of the astute choice of a virgin but fertile and important research area. I also have seen research careers flounder because of the careless choice of an area, perhaps one dominated by your research advisor, one that is crowded, or one that has passed its prime. Overall, you must pursue research that is game-changing.

You have to allow yourself plenty of time to select a research area that you would enjoy working on almost every day as an independent investigator. I spent about 10–12 months (in between writing my Ph.D. thesis) to select a research area. That turned out to be the transport machinery indigenous to the conjunctival epithelial cells. You must run your plan by your research advisor, as I did, to gain critical feedback. That is also the time to reach a mutual understanding with your advisor regarding potential overlap in research. In the long run, you would be better off with devoting time to the new area in which your research independence is unequivocal.

Regarding research collaboration, I was fortunate to meet Kwang-Jin Kim, a superb biomedical engineer in the School of Medicine well known for his work in clarifying the mechanism of ion and fluid transport in the lung. He was very vigorous and critical—the same lineage as Terrence Fletcher, the demanding, perfectionist music teacher in the 2014 movie *Whiplash*. In many ways, he was a surrogate research advisor to my team. Through him, my laboratory branched into pulmonary drug delivery and the development of epithelial cell monolayers for characterizing drug transport mechanisms. In addition to Dr. Kim, I also reached out to colleagues in my department with expertise in computational chemistry, mathematical modeling, immunology, molecular biology, and cell biology in my last research project at USC on mapping the substrate binding domain of the human PepT1 transporter and elucidating its trafficking in epithelial cells. In today's fast-paced, highly competitive research environment,

Proud moments related to professional leadership. (A–C) The CRS workshop on "Peptide and Protein Drug Delivery: The Next 10 Years" in September 1993 in Kyoto, Japan. Dr. Lee co-organized the workshop with his good friend Mitsuru Hashida of Kyoto University. (A) Gathering words of wisdom from former CRS presidents (left to right: Joseph Robinson, Jorge Heller, Ted Roseman, and Nicholas Peppas) by the workshop co-chair. (B) Delivering an opening address at the workshop. (C) Giving a speech before the toast at the workshop dinner. (D) Interview for the AAPS Distinguished Scientists video series by Arthur Mlodozeniec during the AAPS Meeting in San Antonio in 2006. (E) With Louis J. Ignarro, 1998 Nobel Laureate in Physiology or Medicine, before his keynote address at the inaugural Frontier of Drug Development Conference cosponsored by USC and its sister universities in Japan in Pasadena, California, in July 1999.

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an institutional culture that facilitates research collaboration is absolutely essential to sustain peer-reviewed research funding. Finally, mentors are as important as collaborators in advancing one's research and professional career. They are the folks who are well connected and who take an active interest in your professional advancement without expecting anything in return. I'd like to pay tribute to the late Joseph Robinson, who played an indispensable advocacy role in my rise in stature as a statesman in the drug delivery and pharmaceutical research circles.

Q *Between your academic and industry careers in the United States, which one was more fulfilling for you and why?*

A My tenure at USC was by far the most rewarding. I was in the cohort of academic staff whose career advancement was aligned with the rise in stature of USC as a respected research-intensive university. The confidence of the dean, John Biles, and my department head, Jordan Cohen, in my capacity to bring credit to USC was an important factor in my long affiliation with the university. At my peak, I logged over 250,000 air miles and was away from USC (and my family) an aggregate of four months a year lecturing on my research, keynoting research conferences, consulting with industry, and evaluating the quality of academic programs. I found these events eye opening, and the school benefited by having advance knowledge of the latest developments and thinking in pharmacy education and pharmaceutical research elsewhere in the world.

My tenure at ALZA was brief. I was excited to join the company because of the opportunity to do something new and also to have access to the best ideas in drug delivery for translation into innovative therapeutics. Several months after I joined, I found myself at odds with senior management regarding vision, values, level of science, and research direction of my team. Without consulting with anyone, I put the "fail fast, fail early" option into play after learning the reluctance of the president to mediate.

Why did I accept the offer from ALZA in 2003 when in 1978 I turned down several job offers from the pharmaceutical industry? I did, in large part, because of ALZA's reputation as a pioneer in advanced drug delivery and because the time was ripe to rekindle that pioneering spirit. Understanding the regulation of drug transport across the blood-brain barrier and subsequently drug distribution in the brain is a high-risk, high-impact area that would define a new ALZA. I was

Happy moments with colleagues and friends. (A) Receptions at the CRS meeting in Washington DC in 1993 with former Japanese postdoctoral fellows (right to left: Kazuhiro Morimoto, Koyo Nishida, and Hitoshi Sasaki). (B) Celebrating Christmas 1997 at home in California. A snapshot of the tasting panel after one sip of a Swedish Christmas brew concocted extemporaneously by Denny Mahlin. (C) Group photo of Leelab before the reunion dinner in Bourborn Street on the occasion of the AAPS meeting in New Orleans, Louisiana, in 1999. (D) Gathering before the karaoke marathon in Roland Daumesnil's hotel suite on the occasion of the CRS Meeting in Orlando, Florida, on the eve of the presidential transition from Robert Langer to Vincent Lee in 1992. Roland is between Prof. Nagai and Vincent Lee. Next to Prof. Nagai is Vincent's younger brother, Vincent Li. (E) After the conferment of the honorary doctor of science degree at the University of London School of Pharmacy with then-Dean Sandy Florence and their "boss" Kim Briggs, senior editor at Elsevier in 2003.

hoping that the introduction of life sciences would spark the rejuvenation of the company's well respected, but aging, core competency in material science and chemical engineering.

Q *How do you recall the difference in work culture between Upjohn and ALZA?*

A I was a 1976 summer fellow in the laboratory of Joe Turi at Upjohn studying percutaneous drug transport. The environment there was vibrant and collegial. It was indeed a privilege to learn from the world's experts in solubility, mass transport, solid state chemistry, compressibility, stability, and prodrugs, who were on the senior scientific staff. Just about everyone on the senior staff was a regular contributor to the peer-reviewed scientific literature, in addition to putting out drug products on the market. Cutting-edge science was clearly the foundation to product development, in keeping with the company's motto, "Keep the Quality Up."

ALZA had a somewhat different culture. I joined in April 2003, two years after it was acquired by Johnson & Johnson. My perception was that the company was experiencing an identity crisis. It was also under pressure from the head office to come forth with a mechanism to add value to the products marketed by sister companies.

Q *Having spent your entire college education and a good part of your academic and industrial career in the United States, what was your motivation to return to Hong Kong?*

A There are two main reasons. The first is personal: to take care of my 77 year old mother, who was widowed since 1980. The second reason is professional: to learn firsthand the opportunities and challenges in transforming drug discovery and development, healthcare, and professional education, and to determine the role Hong Kong could play.

Q *How do you see the Asian subcontinent being different from the West (North America and Europe) in terms of R&D and business development? What are the some of the challenges?*

A The economic honeymoon in Asia in the past 25 years has created a false pretense that Asia will be the next hub of pharmaceutical innovation. On the positive side, the Asian subcontinent is probably more receptive than the West to new ideas and new business models of drug development, since it has virtually no experience in taking a new drug from discovery to market. On the negative side, there is a shortage or lack of sophisticated know-how in drug development and regulation. This is due principally to a shortage of world-class universities in many Asian countries—except Korea, Singapore, Hong Kong, and Taiwan—to conduct world-leading research and train scientists and engineers to drive the transformation. Consequently, it will be decades before the Asian countries will be an important source of new drugs and new therapeutic concepts. In the near term, Vietnam, Malaysia, Indonesia, and other countries in Southeast Asia may emerge as the home for outsourced manufacturing of pharmaceutical products in facilities that have been upgraded to enable continuous manufacturing, as a replacement for the decade-long more expensive and more error-prone batch manufacturing.

Establishing 3D printing (also called additive manufacturing) as a solution to customizing drug formulations, thereby enabling the fulfillment of precision medicine, has not yet caught on, but it is a drug delivery technology in which Asian countries should claim ownership and leadership. Indeed, formulations designed to compensate for the deterioration in postural balance, manual coordination, swallowing, and cognitive acuity commonly seen in the elderly would be a timely development. Let's not forget China alone could have some 400 million people over 60 years of age by 2050. Therefore, the market demand for such formulations could be substantial.

Q *Compared with the United States, what are some of the challenges faced by research professors in the East? What was it like during the last decade? What changes should have been made?*

A Professors in the East are under relentless pressure to publish in high-impact journals in the endless chase by their home institutions in the QS ranking of world universities. This level of intensity is characteristic of younger universities aspiring to be ranked among the top 50. The University of Hong Kong, the Hong Kong University of Science and Technology, and the Chinese University of Hong Kong have already achieved that status.

To have a steady stream of research of the caliber that meets the editorial standards of *Science, Nature, New England Journal of Medicine*, and the like, several conditions must be met: (1) a critical mass of expertise in the bridging science between drug discovery and drug approval; (2) more than one round of proposal-vetting a year (NIH has three rounds); (3) ability to live up to the Ph.D. fellowship scheme's intention to compete with Oxford, Cambridge, Harvard, Stanford, MIT, Caltech, and the like for high-caliber graduate students; (4) a roadmap of career advancement for the graduates in locations beyond Hong Kong, such as China, Indonesia, Malaysia, and the like; and (5) modernizing the tertiary education infrastructure with respect to flexible time to degree, requirement of course work, and relaxing or eliminating the master's degree requirement for application for admission to a Ph.D. program.

At a more fundamental level, primary and secondary school students should be in an environment where they learn to be interactive, to be critical, to be willing to share their thoughts, ideas, and findings, to think globally, and not to be afraid to fail. Hong Kong students in Grades 3 and 9 are consistently ranked among the top 10 in mathematics and science in the world and, within the past five years, the top five. But what percent of these students in Hong Kong continue to become scientists?

Q *In which direction do you see pharmaceutical R&D heading? In your opinion, what are the paradigm shifts we should expect to see?*

A The turning point in pharmaceutical R&D is the realization that genomics, combinatorial chemistry, and high-throughput screening—advances that focused on increasing the probability of finding new drug targets or discovering new signaling

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pathways—had not resulted in an overnight success in improving the efficiency of drug discovery. While genomics also plays a role in pharmacologic diversity in a patient population, there are human factors that also contribute. The high-risk patient who needs to be monitored may benefit from the creation of a wireless network linking the patient, pharmacist, and physician. Such a network would facilitate real-time monitoring of progress of therapy and timely rendering of corrective actions by the physician, who is likely to delegate it to the pharmacist on the team. As a PD patient, I cannot agree more with the important decision-making role of the patient in determining the therapeutic outcome. This is now part of the Food and Drug Administration Safety and Innovation Act (FDASIA) signed into law in 2012.

The life sciences revolution produces not only tools that enable us to manage the complexity of disease but also biologics (mostly monoclonal antibodies) that have defied conventional wisdom of anticipated poor acceptance by patients because they can only be given by injection. Biologics are an integral part of therapeutics that are expected to account for 17% of total global spending on medicines in 2016, equivalent to $200 billion in total market value. Moreover, seven of the top 10 global medicines by spending will be biologics.

The dilemma healthcare professionals now face is the prohibitive cost of several of these new drugs—many on the order of $10,000 per day or per dose, which may put these miracle drugs out of reach of all but the affluent. That the new head at the Chinese FDA is knowledgeable in economics is a subtle hint on the importance of drug pricing to China.

The business model of drug development is changing as well. Pharmaceutical companies in the 21st century tend to have a more compact and focused portfolio of only a few therapeutic areas. It is still early to tell whether the recent swap of GSK's oncology portfolio with Novartis's vaccine portfolio is a trend setter. As in the case of the airline industry, it is usually the new kids on the block, such as Gilead and Celgene, that outperform the legacy companies. Other changes on the horizon include the merger between a generic company (Actavis) and a big pharma (Allergan) that was initiated by the generic partner. So, the line between brand and generic issue will continue to blur.

Academic staff of the Chinese University of Hong Kong School of Pharmacy taken in the lobby of the current location on Grand Opening Day in 2013. From left to right: Teddy Lam, Chui-ping Lee, Vivian Lee, Susan Ho, Larry Baum, Joyce You, Jennifer Yu, Vincent Lee, Joan Zuo, Keary Zhou, Celeste Ewig, Kenneth To, and Albert Chow. The logo, designed with Vincent Lee's input, depicted the mission of the school in working collaboratively with students as well as the pharmacy profession to apply scientific knowledge to develop and select drug products for patients.

There is as yet a third scenario in the form of a strategic alliance between industry and academia, whereby academia will drive innovations and industry will focus on development, manufacturing, and commercialization. Creative thinking is required of both partners regarding ownership and disposition of intellectual property, oftentimes the hurdle to consummating the partnership. At the industrial level, willingness to share proprietary knowledge, an important step to minimize duplication and dead ends, is imperative.

I would be remiss by not commenting on the changing role of the drug regulatory agencies. I found it exciting to join the FDA in 2004 at the dawn of a historical era of proactive drug regulation, from the launch of the Critical Path Initiative to expand the array of drug development tools to the launch of the Sentinel Initiative to mine adverse drug reactions not detected during phase I–III clinical trials. Regulatory agencies in the future will have a reduced role in inspection and enforcement in exchange for an expanded role in setting priorities for drug registration. These are milestone developments in the long and winding road of drug discovery, development, and regulation.

Q *Please share your progress plans for the Chinese University of Hong Kong.*

A Hong Kong has not fully exploited the "one country, two systems" model of governance. What was once a vibrant city with an abundance of imagination and creativity appeared to be losing its self-confidence, ambition, sense of direction, and optimism of late. People are apprehensive of venturing outside their comfort zone and of taking risks for fear of failure. Such a cautious approach is also reflected in the previous eight budgets developed by the Finance Secretary for Hong Kong. Each budget has a substantial surplus, on the order of HK$60 billion this past fiscal year. Past practice to minimize the size of the surplus was to return a sum to special interest groups, thereby risking the fostering of entitlement and complacency. A better use of the surplus would be to devise a plan to jumpstart new industries, such as the pharmaceutical industry. Pharmaceutical R&D has been on the sideline despite the existence of three world-class universities that can serve as the source of new drugs. The main reasons are the preference of Hong Kong scientists to be self-sufficient, their reluctance to work collaboratively, the high risk, and the excessively long time. An equally important reason is underestimation or unawareness of the stringent requirements of formulation development and manufacture. These requirements are within the know-how of the school, and that must be publicized. Indeed, the School of Pharmacy is more than a school dedicated to training pharmacists. ■

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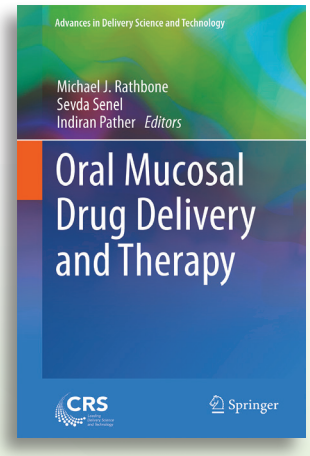

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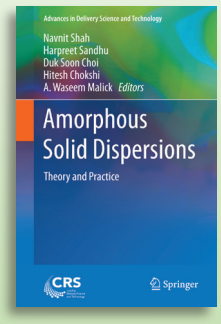

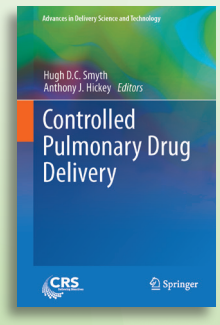

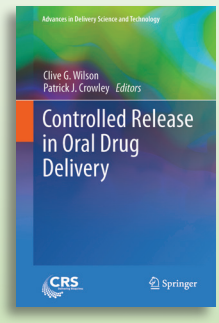

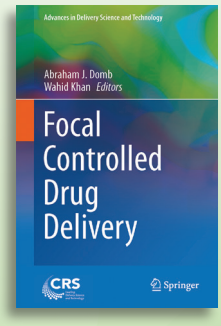

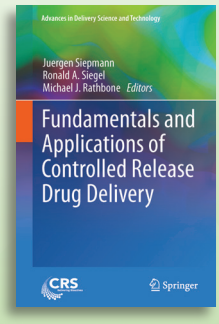

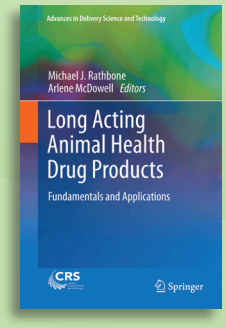

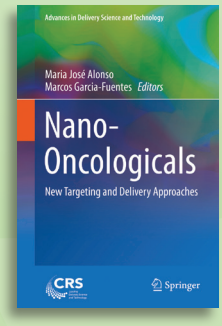

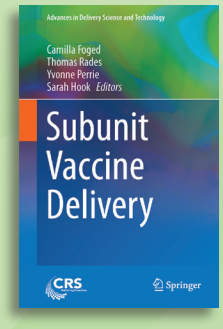

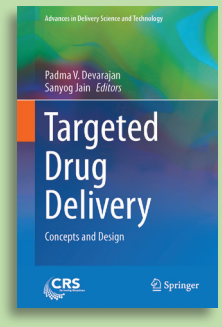

CRS members qualify for a 25% discount on all books in the *Advances in Delivery Science and Technology* series from CRS, along with all Springer book titles if you purchase through Springer's online site and use the exclusive CRS member discount token when ordering. CRS members must sign in to the CRS site to gain access to the discount token before ordering at the Springer site.

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2015 CRS ANNUAL MEETING

Giving You MORE

The CRS Annual Meeting brings renowned researchers, industry experts, and young scientists together from around the globe to discover customized approaches and high-value solutions in delivery science and technology. For 2015, the Annual Meeting Program Committee (AMPC) and Annual Meeting Committee have created a brand new meeting event—a dynamic exposition, targeted networking events, and a compelling and interactive scientific program. This meeting promises to deliver MORE than ever before. So make plans to join CRS in Edinburgh, Scotland, to learn more on the latest in cutting-edge research and discover more new technologies in delivery science and delivery applications.

MORE Science

▸ More Plenaries

CRS is known for its world-class plenary speakers, and we are excited that the 2015 program will offer **more** of them. CRS will showcase an internationally recognized plenary speaker on each day of the meeting:

Polymers and Nanomedicines – The Promises and Pitfalls of New Materials, **Cameron Alexander**, School of Pharmacy, University of Nottingham, United Kingdom

Global Efforts and Successes in Needle-Free Peptide Delivery, **María José Alonso**, University of Santiago de Compostela, Spain, and coordinator of the TRANS-INT European Consortium

Ligand-Directed Therapy and Molecular Imaging Based on In Vivo Phage Display Technology, **Renata Pasqualini**, University of New Mexico Cancer Center, U.S.A.

Customized Drug Delivery: A Personal Odyssey, **Vincent H. L. Lee**, School of Pharmacy, Faculty of Medicine, Chinese University of Hong Kong

In addition, there will also be a special address from the 2015 CRS Foundation Travel Grant Program namesake and CRS past president, **Nicholas A. Peppas**, The University of Texas at Austin, U.S.A. Come hear Prof. Peppas speak on intelligent polymer hydrogels.

▸▸▸ Register by May 14, 2015, and Save!

More Posters

This year you can experience this exceptional poster session in more ways. At the meeting, see over 950 posters; before and during the meeting, listen to two-minute poster podcasts with the meeting app, and review the abstracts online; and after the meeting view the posters online. There are more ways than ever to access this vital research.

This year the record-breaking number of posters are categorized according to core area. As always, authors will be present during dedicated sessions to discuss their research and answer questions. The 2015 poster sessions are:

1. Delivery of Proteins, Peptides, and Vaccines
2. Delivery Science in Cosmetics, Personal Care, and Household Products
3. Encapsulation for Industrial Applications
4. Manufacture, Characterization, Measurement, and Stability
5. Micro- and Nanoparticle Delivery
6. Oral Delivery for Food and Pharma
7. Parenteral Controlled Release
8. Regional Delivery
9. RNA and DNA Delivery
10. Topical and Transdermal Delivery

More Interaction

Scientific Sessions form the core of the annual meeting, and this year they have been redesigned for greater exchange of information. Each scientific session will feature two invited speakers—one from industry and one from academia. These will be followed by five of our new Research Highlight presentations. These new presentations will offer you more ways to discover the science with both a quick oral presentation of highlights and a poster with deeper insights. Additionally, each scientific session will close with group discussion moderated by a luminary of the science. The 2015 scientific sessions are:

Monday, July 27

- Delivery of Vaccines
- Drug Delivery to the Brain
- Encapsulation for Industrial Applications
- Manufacture, Characterization, Measurement, and Stability
- Modulated and Responsive Delivery Systems
- Oral Delivery for Food
- Respiratory Drug Delivery
- Transdermal Delivery

Tuesday, July 28

- Delivery of Peptides and Proteins
- Delivery Science in Cosmetics, Personal Care, and Household Products
- *In Vivo* Nucleic Acid Delivery
- Nano-Sized Carriers for Small-Molecule Oncology Drugs
- Ocular Drug Delivery
- Oral Drug Delivery
- Parenteral Delivery Technologies
- siRNA and mRNA Delivery

Wednesday, July 29

- Drug Delivery in Tissue Engineering
- Formulating Oral Solid Dosage Forms to Enhance Drug Delivery
- Nanocarriers for Combined Delivery
- Nanosystems for Non-Oncology Drug Delivery

More Innovation

CRS is all about the business of delivery science—taking innovative ideas and technologies into the commercial sector. And during the Innovation Sunday sessions you will get important new information on companies and technologies as well as great opportunities for networking. The innovation sessions include the **Technology Forums,** where you gain in-depth information presented by the hosting company; the **Soapbox Sessions,** which are fast paced and offer a quick glimpse of the most innovative technologies and products in development today; and the **Industry Roundtable** of CEOs discussing the latest in the industry's shift to patient-centric care.

More Viewpoints

The mini-symposia showcase the knowledge and individual views of three invited experts in a specific area of delivery science and technology. The mini-symposia sessions are:

- Cost-Effective Encapsulation for Industrial Applications: Limitations and Solutions
- European Technology Platform on Nanomedicine: Translation of Nanomedicines
- Modeling and Simulation of Oral Absorption – A Progress Report from the EU/IMI Project OrBiTo
- Next-Generation Vaccine Development and Delivery Technologies
- Therapeutic Cancer Nanomedicines

Workshops offer focused presentations by noted speakers in a small group setting, so group interaction and even some hands-on experience is possible. The premeeting workshops include:

- Advanced Pulmonary Drug Delivery: From Generating Aerosols to Overcoming Biological Barriers
- Delivery of Therapeutic Bioconjugates: From Polymer Conjugates to Antibody-Drug Conjugates
- Introduction to Encapsulation and Controlled Release Technologies
- Ocular Drug Delivery – Challenges of Matching New Technologies with Drug Pharmacokinetics

42nd CRS Annual Meeting & Exposition continued on page 12

MORE Connections

More Networking

This year's program is set to offer networking in and out of the session rooms. In addition to the moderated Q&A sessions, you can expand your network through the C&DP lunch and PSAH happy hour, the Young Scientists "Scotch Whisky Experience" evening, and the Women in Science Event with featured speaker Begoña Carreño, Novartis Pharmaceuticals, "There Is Light on the Dark Side: A Journey Through Big Pharma." New this year will be an opportunity for students and postdocs to connect with a VIP in the science through the Lunch with a Luminary program. This year's featured luminaries will be Vincent H. L. Lee and Nicholas A. Peppas.

More Prospects

The CRS 2015 Exhibition will deliver more quality prospects. You can reach more than 1,300 influential scientists working in drug delivery, consumer and diversified products, and preclinical sciences and animal health who are looking for new solutions and technologies. Connect with the global delivery science community with an exhibit.

Exhibit space is available but limited. Contact Philippe Pinzi at ppinzi@scisoc.org or +32 2 743 15 40.

More Fun

To close out your new meeting experience and cement your new connections, we've added a new party!

Included in most registration fee categories is the Scottish Gathering or "ceilidh." Held at the Assembly Rooms, a UNESCO World Heritage site that has been the home of grand assemblies and musical performances since 1787, the ceilidh will include drinks, hors d'oeuvres, and dancing—Scottish style! Limited reception tickets are also available for purchase with guest, single day, and exhibitor registrations. Early purchase is encouraged.

2015 Annual Meeting Program Committee

Chair:
Justin Hanes, Johns Hopkins University, U.S.A.

Deputy Chair:
Kinam Park, Purdue University, U.S.A.

Team Members:
Adah Almutairi, University of California, U.S.A.
You Han Bae, University of Utah, U.S.A.
Igor Bodnár, Firmenich, Switzerland
David Brayden, University College Dublin, Ireland
Doug Dale, DuPont Industrial Biosciences, U.S.A.
Bill Lambert, MedImmune, U.S.A.
Yvonne Perrie, Aston University, United Kingdom
Suzie Pun, University of Washington, U.S.A.
Ilva Rupenthal, University of Auckland, New Zealand
Ron Smith, Merck & Company, Inc., U.S.A.

2015 CRS Annual Meeting Exhibitors

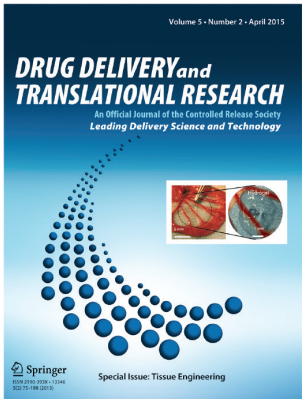
Come to the Exposition Hall for discovery, solutions, opportunities, and refreshments! Kicking off with the Sunday evening Exposition Grand Opening & Welcome Reception, the Exposition Hall will also be open Monday and Tuesday as the central hub for one-to-one networking, program breaks, and refreshments.

Adhesives Research/ARx, LLC
Advanced Polymer Materials Inc.
Akina, Inc. PolySciTech Division
Avanti Polar Lipids Inc.
BASF SE
Bend Research-A Division of Capsugel Dosage Form Solutions
Buchi Labortechnik AG
Caleva Process Solutions
Captisol
Catalent Pharma Solutions
Celanese
Colorcon
Corbion Purac Biomaterials
CordenPharma
Delta ModTech
Dissolution Technologies
Drug Development & Delivery
DURECT Corp./Lactel Absorbable Polymers
Evonik Industries AG
Freund-Vector Corp.
Gattefossé
Gaylord Chemical Company
Hanson Research
MedPharm
Merck Millipore
Mott Corporation
OctoPlus N.V.
Pantec Biosolutions AG
Pharmaceutical Technology
PharmaCircle LLC
Pierre Fabre Medicament—Supercritical Fluids Division
Polymun Scientific GmbH
Polysciences Inc.
Precision NanoSystems, Inc.
ProMed Pharma LLC
SE Pharma & Food Distribution GmbH
Simcyp (A Certara Company)
Simulations Plus
SOTAX Ltd.
Southwest Research Institute
Springer
Stable Micro Systems Ltd.
Wyatt Technology Corporation

▶▶▶ Register today at controlledreleasesociety.org/meeting

Drug Delivery and Translational Research Update

Vinod Labhasetwar, Editor-in-Chief, Cleveland Clinic, Cleveland, Ohio, U.S.A.



DDTR in PubMed

DDTR has been accepted for indexing in PubMed. Applications for indexing in PubMed are reviewed by the National Library of Medicine, which uses an advisory committee (Literature Selection Technical Review Committee) chartered by the National Institutes of Health (NIH). The decision is based on several stringent criteria including timely publication of issues, quality of papers published, value of the journal, credentials of the editorial team, ethical compliance, and so on. The success rate has been sliding down each year; it was only 12% in 2014. If the application is rejected, the journal cannot reapply for two years. We are glad that *DDTR* made it in on the first attempt.

Currently, NIH-funded and a few other agency-funded research articles published in *DDTR* are indexed in PubMed. With approval of our application, all the articles published in *DDTR* will be indexed in PubMed. Because PubMed is a widely searched database, we hope that it will further increase citations of the articles published in the journal.

2014 _DDTR_ Outstanding Research Paper Award Winner

The Selection Committee and CRS are pleased to announce the following paper published in *DDTR* during 2014 for the award. Criteria such as the translation nature of the research, overall impact, and significance of the study were considered in the selection process. The award is jointly sponsored by Springer and CRS. The corresponding authors will be recognized at the 2015 CRS Annual Meeting in Edinburgh, Scotland, on July 26–29. Please join us in congratulating the authors for their outstanding achievement.

Multifunctional Polyion Complex Micelle Featuring Enhanced Stability, Targetability, and Endosome Escapability for Systemic siRNA Delivery to Subcutaneous Model of Lung Cancer

Authors: Hyun Jin Kim, Takehiko Ishii, Meng Zheng, Sumiyo Watanabe, Kazuko Toh, Yu Matsumoto, Nobuhiro Nishiyama, Kanjiro Miyata, and Kazunori Kataoka
Drug Delivery and Translational Research 4: 50-60 (2014)

In this paper, the authors have synthesized a novel block copolymer for siRNA delivery. The resulting polymer was confirmed to form siRNA-loaded micelles with a diameter of <50 nm and a narrow size distribution. These micelles were shown to achieve sequence-specific gene silencing and tumor growth inhibition in a subcutaneous lung model following systemic administration.

About the Corresponding Authors

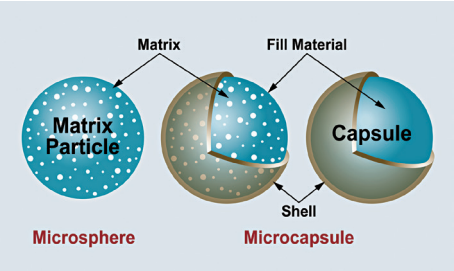
Kanjiro Miyata received his Ph.D. under the supervision of Kazunori Kataoka in the Department of Materials Engineering, Graduate School of Engineering, University of Tokyo, in 2006. From 2006 to 2009, he worked as an assistant professor in the Department of Bioengineering. In 2009, he moved to the Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, University of Tokyo. Since 2013, he has been an associate professor in the research center. He has received several young scientist awards: the Award for Encouragement of Research in Polymer Science from the Society of Polymer Science in 2009, the Award for Young Investigator from the Japanese Society for Biomaterials in 2012, and the Young Investigator Award from the Japan Society of Drug Delivery System in 2015. His main research interest is related to smart polymeric nanocarriers for nucleic acid delivery.

Kazunori Kataoka is a professor of biomaterials at the Graduate School of Engineering, University of Tokyo, Japan. Since 2004, he has been appointed to a joint position in the Graduate School of Medicine as a professor of clinical biotechnology at the Center for Disease Biology and Integrative Medicine. He received his B.Eng. (1974) and Ph.D. (1979) from the University of Tokyo. He has received numerous awards, including the Founder's Award from CRS (2008), the Science and Technology Prize awarded by the Minister of Education, Culture, Sports, Science and Technology, Japan (2010), Humboldt Research Award from the Alexander von Humboldt Foundation (2012), Leo Esaki Prize (2012), Lifetime Achievement Award from *Journal of Drug Targeting*, and Gutenberg Research Award from Johannes Gutenberg University Mainz (2014). He served as president of the Society of Polymer Science, Japan (2010–2012) and president of CRS (2012–2013). He has been elected as a fellow of the American Institute of Medical and Biological Engineering (AIMBE) (1999), a fellow of the International Union of Societies for Biomaterials Science and Engineering (IUSBSE) (2004), a founding fellow of the CRS College of the Fellows (2010), and a member of the Science Council of Japan (2006). He is on the editorial and advisory boards of 14 international journals, and he has been the editor of *Journal of Biomaterials Science, Polymer Edition* since 2004. His current major research interest is supramolecular materials for nanobiotechnology, particularly focusing on drug and gene targeting, and he has published more than 500 papers with an *h*-index of 113 (Google Scholar). ■

Introduction to Microencapsulation Workshop

James Oxley[1] and Jean Antoine Meiners[2]

Several workshops are available to attendees of the 2015 Controlled Release Society Annual Meeting in Edinburgh, Scotland, this coming July. One of the workshops, "Introduction to Microencapsulation," is a frequent offering that draws a large and diversified audience. Technology experts will provide an introduction to state-of-the-art microencapsulation techniques used throughout multiple industries for controlled release applications, followed by lab-scale demonstration of many of the discussed processes.



Courtesy of Southwest Research Institute.

Many controlled release systems are based on standard microencapsulation technologies, such as spray drying, fluid bed coating, or emulsion-based encapsulation systems. While advances in these areas continue to broaden the applications of encapsulation and expand process limitations, the fundamentals remain unchanged. It is important for everyone active in the field of controlled release or microencapsulation to have a basic understanding of the available processes. This workshop is applicable to a wide range of attendees, from a graduate student looking to get started in the field of encapsulation to a corporate executive expanding their company portfolio into encapsulated products. Scientists partially active in the field can also gain new insight from the workshop by learning about other processes.

Multiple industries benefit from the use of microencapsulation, and the content of this workshop can be applied across these industries, including pharmaceuticals, nutraceuticals, food, cosmetics, consumer products, agriculture, paints and coatings, oil and gas, and many other industrial applications. Representatives from all industries, in addition to academic institutes, are encouraged to attend for the chance both to gain basic knowledge on encapsulation processes and to share ideas regarding controlled release solutions that may transcend multiple applications and industries.

The workshop will span one and a half days, with the first day focused on introductory lectures. These lectures will cover atomization, spray coating, coextrusion, emulsion-based processes, and nanoencapsulation. An introduction to atomization will include discussion of spray drying, spray chilling, and prilling. Coextrusion discussion will focus on annular jet atomization and the different subsets of the available related technologies. Emulsion-based processes to be discussed include coacervation, *in situ* polymerization, and interfacial polymerization. Nanoencapsulation will be covered at a basic level, introducing attendees to the array of technologies currently used for preparing submicron capsules. In addition to discussion of the processes, lectures will be provided to address the selection of materials and characterization of microcapsules. The first day will conclude with a discussion of the common challenges and the future of microencapsulation.

The lectures will provide an overview of the processes, strengths, weaknesses, and basic understanding for attendees to begin assessing if a process is suitable for their applications. Lectures will be presented by the following industry leaders:

- James Oxley, Principal Scientist, Southwest Research Institute, San Antonio, TX, U.S.A.
- Jean Antoine Meiners, Chief Scientific Officer, MCC Laboratoire Meiners, Colombier, Switzerland
- Irwin Jacobs, Managing Director, Jacobs Controlled Release, St. Louis, MO, U.S.A.
- Klaus Last, Head of Microencapsulation, Follmann & Co. GmbH, Minden, Germany

Combined, the lecturers represent 75 years of direct experience with encapsulation processes. In addition to providing the background knowledge of these processes, they will provide insight into their personal experience with the processes across multiple industries.

The second day will provide a half day of observing multiple laboratory-scale encapsulation processes. Atomization technologies will be demonstrated by BÜCHI Labortechnik AG and operation of their B-290 Mini Spray Dryer and Encapsulator B-390. Spray coating will be demonstrated by Caleva Process Solutions and their MCD-2 Laboratory Tablet Coater. Representatives from MCC Laboratoire Meiners will provide a demonstration of complex coacervation using standard laboratory equipment. Combined, these demonstrations will collectively reinforce the lecture content and provide attendees with direct observations of the processes as they are being operated.

The combination of classroom instruction and process demonstrations will empower attendees with the basic knowledge of processes available to prepare capsules from nanometers to millimeters with varying characteristics. The assembly of attendees from varying backgrounds and industries will contribute to a unique forum for discussion of challenges and how microencapsulation can be applied across multiple industries. As a precursor to the annual meeting, the knowledge from this workshop can be carried forward into the technical sessions and contribute to the overall value of the meeting. Workshop registration is available through the annual meeting registration process. Register early to secure your spot in the workshop! ■

1 Southwest Research Institute, San Antonio, TX, U.S.A.
2 MCC Laboratoire Meiners, Colombier, Switzerland.

2015 CRS Election: Cast Your Ballot

The 2015 CRS Election is open April 9–30, and all members are encouraged to vote. Following the call for nominations that was sent to the membership, the CRS Nominating Committee formalized the ballot based on the needs of the organization for both the CRS Board and the Board of Scientific Advisors (BSA). The CRS Board ballot was sent to the membership for the petition period. Because no members were added to the ballot through the petition process, Ruth Schmid will take the position of President-Elect. Electronic ballots have been sent to all eligible voting members of CRS along with biographies and vision statements from all candidates. The newly elected Board and BSA members will take their positions in July at the conclusion of the 2015 CRS Annual Meeting.

CRS Board

President-Elect

Ruth Schmid
SINTEF, Norway

Treasurer-Elect

Christine Allen
University of Toronto, Canada

Julius Remenar
Alkermes Pharma Ireland Ltd., U.S.A.

Secretary

Ben Boyd
Monash University, Australia

Andy Lewis
Ipsen, France

Director-at-Large (Two Open Positions)

Doug Dale
DuPont Industrial Biosciences, U.S.A.

Justin Hanes
Johns Hopkins University, U.S.A.

Nicole Papen-Botterhuis
TNO, Netherlands

Christian Seiler
Pharma XP Consulting Ltd., United Kingdom

Board of Scientific Advisors

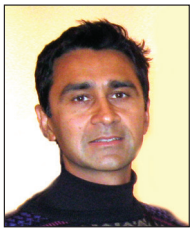
In addition to the CRS Board positions, the membership will also vote on the seven open BSA positions. The BSA is charged with providing advice to CRS on all aspects of the science and technology of delivery so that CRS will fulfill its mission. The candidates for the BSA are:

Daniel Bar-Shalom
University of Copenhagen, Denmark

Craig Bunt
Lincoln University, New Zealand

Peter Cheifetz
Merial Inc., U.S.A.

Weiguo Dai
Johnson & Johnson, U.S.A.



Neil Desai
Abraxis Bioscience, U.S.A.

Michael Doschak
University of Alberta, Canada

Hideyoshi Harashima
Hokkaido University, Japan

Arlene McDowell
University of Otago, New Zealand

Jean-Antoine Meiners
Laboratoire Meiners Sàrl, Switzerland

Ulrik Rahbek
Novo Nordisk A/S, Denmark

Ming-Thau Sheu
Taipei Medical University, Taiwan

Arto Urtti
University of Helsinki, Finland

Ian Tucker, CRS Past President, will oversee the 2015 election due to Christine Allen, current CRS Secretary, being on the ballot. Any questions related to the election should be directed to Prof. Tucker, ian.tucker@otago.ac.nz.

Articles and Websites of Interest in Animal Models of Diseases, Cross-Species Comparisons, and "One Health"

Compiled and edited by Terry Bowersock[a] and David Brayden[b]

Effective treatment for Niemann–Pick disease type C (NPC) has been identified in cats and could benefit humans.[1] NPC has a devastating effect on school age children, eventually resulting in death by age 20. The disease is referred to as "childhood Alzheimer's" due to the physical and mental deterioration of the patients. NPC is a lysosomal storage disease due to mutations in the NPC1 gene leading to changes in lipids and hepatic as well as neurological disease. Currently, there is no approved treatment for this disease. Subcutaneous administration of 2-hydroxy-propyl-β-cyclodextrin (HPβCD), an agent that removes cholesterol from cells *in vitro*, in cats with NPC, which is a similar naturally occurring disease with similar progression to human disease, reduced hepatic function. However, doses of this agent that reduced neurological disease induced pulmonary toxicity. Intra cisterna magna injection of HPβCD into cats prior to onset of symptoms of disease prevented initiation of cerebellar dysfunction for more than a year. Untreated cats died before 6 months of age, but treated cats appeared normal at 6 months of age. Moreover, when administered in a similar manner to cats with NPC, cats lived longer, had less brain damage, and slowed disease progression. This method of treatment did result in some hearing loss. Overall, direct administration of HPβCD into the central nervous system offers hope for control of NPC in children, and a phase 1 trial started last year.

Limiting food intake and caloric restriction in species from *Caenorhabditis elegans* to primates can improve metabolic dysfunction and improve healthy aging.[2] On the downside, caloric restriction can also decrease fertility and immune function. There is a new study by these authors showing a therapeutic alternative to caloric restriction that can still have the positive effects without the undesired side effects. Activated protein kinase (AMPK) acts as a fuel sensor monitoring energy levels in cells. It can also inhibit a protein (CRTC-1) in neurons that affects the production of a neurotransmitter. Altering the AMPK pathway in a subset of neurons can be enough to override its effect on metabolism and cell life in other tissues. Amazingly, aging could be altered by what the animal perceived they were eating rather than what they actually ate calorie-wise. Therefore, it is possible to manipulate an energy sensing pathway in an animal to cause it to perceive that its cells are in a low calorie intake state, even if it is actually eating normally and has normal or high caloric intake. Therapeutics could be produced to target these energy sensing cells to modulate age related diseases such as cancer and neurodegeneration without the need for caloric restriction.

TREM2 regulates microglial cell activation in response to demyelination *in vivo*.[3,4] Using a mouse model, scientists have found a potential target (TREM2) protein on the surface of brain cells that may help in the treatment of multiple sclerosis and Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and other neurological diseases. This protein binds to waste that builds up in the brain in the course of daily mentation and stimulates a misdirected immune response which attacks brain cells. Too much waste present for too long a period of time equals neurological disease. Alzheimer's plaques build up more slowly in mouse brains that have a defective version of the TREM2 protein. TREM2 protein deficient mice also could not clean up debris from nerve damage similar to that seen in multiple sclerosis. Therefore, scientists are looking into a way to stimulate TREM2 activity to prevent or reduce damage in neurological diseases. Alzheimer's susceptible mice lacking the TREM2 gene have significantly increased presence of plaques. Microglia groups surround amyloid plaques when TREM2 is present theoretically to prepare to remove plaques. If mice lacking the TREM2 gene are given a compound that damages myelin in a manner seen in multiple sclerosis patients, debris is seen up to 12 weeks later, in contrast to mice with the TREM2 gene, where damaged myelin is cleared. Mice with uncontrolled myelin damage also had motor control aberrations. These studies suggest that TREM2 detects amyloid beta and damaged neurons, mediates removal of damaged neural cells, and keeps microglia from self-destruction as debris is cleared from brain.

The FDA has banned the sale of stem cells for human medicine. With the exception of bone marrow transplants, stem cell therapy has not been approved for U.S. patients. However, in veterinary medicine treatment of animals is not restricted to this extent. This allows for researchers to investigate stem cell therapies for a variety of diseases that benefit the animals directly but also in many cases can provide insights into potential applications to human diseases.[5] At Cummings School of Veterinary Medicine at Tufts University, with support from the Shipley Foundation, researchers plan to test stem cell therapy for spinal cord injuries/paralysis, kidney disease, and a brain

[a] Zoetis, LLC (formerly Pfizer Animal Health), U.S.A.
[b] University College Dublin, Ireland.

inflammation disease similar to multiple sclerosis in humans. Cummings SVM has filed pilot stem cell studies with the FDA Center for Veterinary Medicine to create an important transparent public record of steps used for stem cell research, from harvest to growth and use in animals. FDA provides oversight, review, and suggestions for improving protocols, as well as suggestions on conduct of the trials. The intent is that research done in this manner will provide a national resource on how well stem cells work *in vivo* and what animal diseases are the best models for human diseases for predicting success in human therapy. Performing testing in dogs costs $500 per patient, compared with $20,000 to $100,000 per patient in human trials. Since dogs are anatomically and physiologically similar to humans, results of studies in dogs are expected to be highly predictive of treatment success in humans.

An ongoing trial in dogs is investigating the use of mesenchymal stem cells (from dog patients themselves) to treat anal furunculosis in dogs, which is similar to Crohn's disease in humans. The furunculosis is thought to be autoimmune in basis, requiring potent immunosuppressants to control the disease. Unfortunately, this can be a very expensive treatment. The use of stem cells has shown promise, reducing the severity of disease 30–70% in four initial patients. Patients could reduce dependence on other drugs and clinically were able to recover activities they had lost, such as the ability to sit on their hindquarters. Follow-up studies are planned to examine the use of human embryonic mesenchymal stem cells as a consistent source for treating a wide number of animals.

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Ocular Drug Delivery: Eye on Innovation

Ilva D. Rupenthal[a] and Michael O'Rourke[b]

Introduction

One would think that a small organ such as the eye that is readily accessible from the outside of the body would be easy to treat. However, the eye has a number of protective barriers in place that pose major challenges to effective drug delivery. Conventional eye drops, for example, the most common method of treating anterior segment diseases, generally result in less than 5% of the applied dose reaching the ocular tissues. This is mainly because of the fast nasolacrimal drainage and the poor permeation across the sandwich-like structure of the cornea, with the lipophilic corneal epithelium being the main penetration barrier. This not only leads to low efficacy and poor patient compliance but can also pose significant risks owing to systemic absorption and associated side effects of the majority of the given dose. To improve the efficacy of topical ocular formulations, researchers have focused on two strategies: 1) to increase the corneal residence time using viscosity-enhancing, mucoadhesive, particulate, and/or *in situ* gelling systems; and 2) to increase the corneal permeability using penetration enhancers, prodrugs, and colloidal systems such as nanoparticles and liposomes. Although many of these have been researched over the past decades with some improvements in the treatment of anterior segment diseases, they are unable to deliver sufficiently high concentrations to the back of the eye.

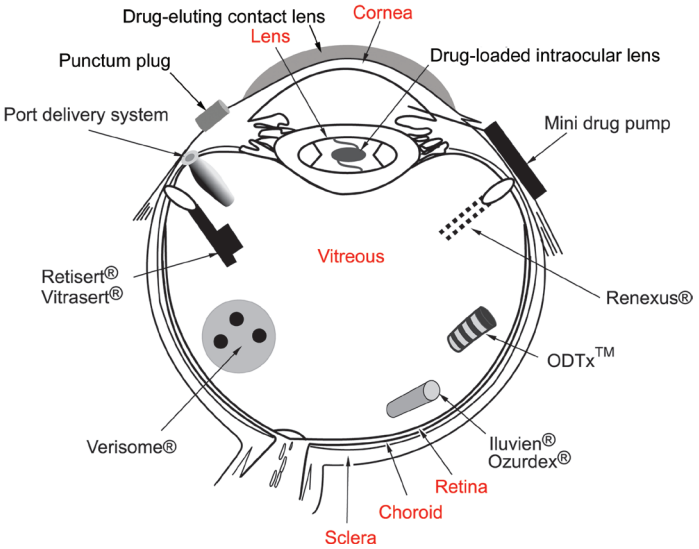

Figure 1. *Overview of the ocular structures and some recent delivery technologies (modified with permission from Elsevier and ONdrugDelivery Magazine [2,3]).*

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The gold standard to treat posterior segment conditions such as wet age-related macular degeneration (AMD) is currently intravitreal injection of the drug-containing solution. Although a relatively site-specific application into the confined vitreal space, injected drugs face elimination processes and need to diffuse through the negatively charged vitreous before crossing the inner limiting membrane to reach the retina. When aiming to reach the choroid, additional permeation barriers such as the retinal pigment epithelium and Bruch's membrane have to be crossed. Thus, periocular injection may offer a more direct route for choroidal drug delivery with the sclera allowing molecules up to 20 kDa to permeate. Moreover, larger volumes can be injected into the periocular space (≤1 mL compared with ≤100 µL intravitreally). Even more localized are suprachoroidal injections using microneedles (Clearside Biomedical), which allow the drug to spread between sclera and choroid. The injection volume is hereby limited to ≤35 µL with simple drug solutions eliminated relatively quickly. However, injecting drug-loaded particles and/or *in situ* gelling systems into this space could offer localized sustained release in the future.[1] Finally, the active could also be administered systemically; however, generally less than 2% of the administered dose reaches the ocular tissues, mainly owing to the tight blood-retinal barrier. An overview of the ocular structures and some of the recent delivery technologies that will be further discussed in this article is given in Figure 1.

Recent Progress in Drug Delivery to the Front of the Eye

While a vast number of approaches have been explored over the past decades to increase precorneal retention and/or corneal permeation, only a limited number of advanced drug delivery systems have actually entered the market. These include prodrug-based eye drops such as Allergan's Propine® from the 1970s, ion-exchange resin particle-based Betoptic® S, the membrane-controlled reservoir system Ocusert®, and *in situ* gelling eye drops such as gellan gum based Timoptic® XE and xanthan gum based Timolol GFS®. However, over the last few years there has been an enormous increase in novel and exciting approaches being researched and/or having entered into clinical trials. Novaliq, for example, is developing topical ocular formulations based on semifluorinated alkanes particularly suitable for the delivery of poorly soluble drugs such a cyclosporine A, with the added advantage of not requiring preservatives and lubricating the ocular surface, both aspects of particular benefit in the treatment of dry eye.[3] Kala Pharmaceuticals is investigating mucus penetrating particles that allow efficient penetration of the tear film mucin layer, the first defense mechanism encountered after topical administration.[4] Envisia Therapeutics is investigating a PRINT-based biodegradable polymer rod intended for intracameral injection for three to eight months of drug delivery (Figure 2).[4] Currently in clinical trials are also three prostaglandin analog-containing punctum plugs (Ocular Therapeutix, QLT, and Mati Therapeutics) all delivering their

cargo over three months, with the Ocular Therapeutix system containing an additional visualization aid to monitor plug retention.[5]

Drug-eluting contact lenses have also recently gained considerable interest for drug delivery to the anterior segment. Drug loading approaches hereby include simple soaking of the lens in the drug solution, incorporation of particles, or molecular imprinting, with the latter two having shown drug delivery for up to one month. Besides refractive and drug delivery capabilities, soft contact lenses have also been investigated as sensors for glucose levels (Google) and intraocular pressure (IOP), with the Triggerfish® from Sensimed able to telemetrically monitor the IOP over 24 h.[6] Similar to currently utilized glucose-sensing insulin pumps, one could thus imagine a combinatory sensing and drug-eluting device able to release the drug in response to a physiological parameter such as an increase in the IOP, enabling patient-specific treatment. A related concept is currently utilized in the Replenish MicroPump™ system, which contains a fluidic flow sensor, a bidirectional telemetry system for wireless programming, and a microcontroller allowing preprogrammed administration of nanoliter-sized doses. With the addition of a precise pressure sensor, this technology could serve as a closed-loop system whereby an increase in the IOP would initiate on-demand drug release.[5]

Recent Progress in Drug Delivery to the Back of the Eye

The gold standard to treat posterior segment conditions remains intravitreal injection, which delivers the drug directly into the eye but may be associated with poor patient compliance and possible complications such as cataract formation and retinal detachment. However, four sustained release implants have also made it onto the market so far. These include nonbiodegradable Vitrasert®, a ganciclovir-containing scleral implant approved in 1996 for the treatment of CMV retinitis, and Retisert®, containing fluocinolone acetonide approved for the treatment of noninfectious posterior uveitis in 2005. Just recently, the FDA approved Iluvien®, also a nonbiodegradable implant (polyimide tube with membrane caps), which is injected into the vitreous using a 25G needle rather than being sutured into the sclera. This implant can deliver fluocinolone acetonide over three years for the treatment of diabetic macula edema (DME). The first ever biodegradable intravitreal implant, Ozurdex®, was approved in 2009 and consists of a PLGA-based rod containing dexamethasone for the treatment of DME, retinal vein occlusion, and posterior uveitis. Also based on this biodegradable polymer, GrayBug is currently investigating a proprietary PLGA-based technology proven to reduce the inflammation seen with conventional PLGA systems, with their lead product for wet AMD treatment targeted to last up to six months.[7] Spun out from the world-renowned Wilmer Eye Institute at the Johns Hopkins University School of Medicine, GrayBug is developing long-lasting ophthalmic drug products that can reduce the frequency of intravitreal injections needed to treat chronic ocular diseases, for both small and large molecules. In addition, the company continues to expand its polymer-based drug delivery technology portfolio for additional ophthalmic indications.

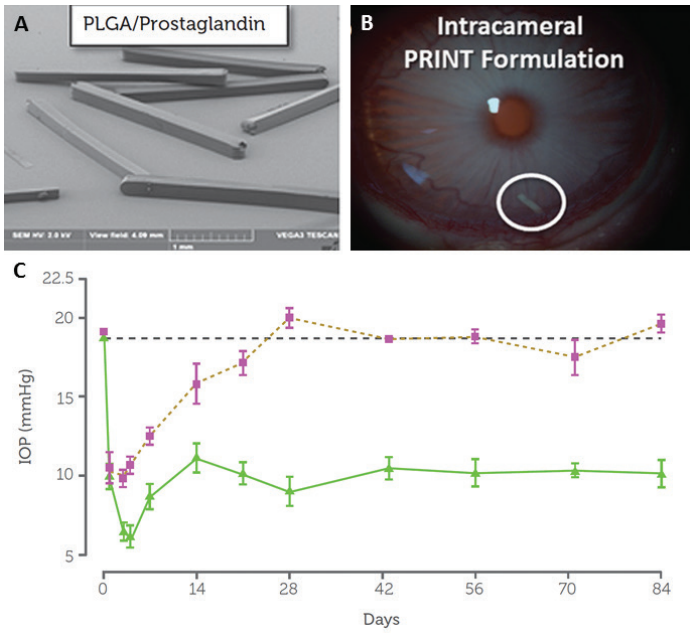

Figure 2. *(A) Envisia PRINT technology-based intracameral implant. (B) Implant injected into New Zealand white rabbits. (C) IOP-lowering effect in normotensive beagle dogs (green: ENV55-8, purple: placebo) (modified with permission from Envisia and ONdrugDelivery Magazine[4]).*

In addition to Envisia's intracameral implant discussed in the previous section, the ENV705 system allows bevacizumab release over three to six months.[4] Another platform technology, Tethadur by pSivida, is based on a suspension of micronized particles of oxidized mesoporous silicon, which slowly dissolve to form silicic acid, providing electrostatic interactions between the slightly acidic particles and the anionic therapeutic. The size of the pores can hereby control the release rate, with smaller pores resulting in more sustained release.[3] Moreover, the EySite-InjecT™ encapsulates by Integral BioSystems are biodegradable, precisely tunable sustained release systems that can be adminis-

NEW – CRS Ocular Delivery LinkedIn Subgroup – Join Today

This group provides a networking platform for scientists from both industry and academia to share experiences, communicate lessons learned, and exchange information regarding novel biomaterials, formulations, delivery technologies, ocular pharmacokinetics, and regulatory issues related to the development of ocular drug delivery systems. The mission of this group is to facilitate the understanding of key factors that influence effective drug delivery to the target tissues of the eye. Members are encouraged to share links on the latest developments, high quality publications, and relevant meetings in the area of ocular drug delivery.

Scientifically Speaking Rupenthal continued on page 20

Scientifically Speaking Rupenthal continued from page 19

tered into the suprachoroidal, intravitreal, or subconjunctival space.[3] Although the majority of the aforementioned particle systems are preformed, the Verisome® technology, based on carbonates, tocopherol, and citrate esters, allows implant formation *in situ* once in contact with the aqueous vitreous environment. Depending on the volume of the formulation injected, drug levels can be maintained for up to 12 months. A different concept is utilized by Zordera, which has developed a nanoporous film device consisting of a drug pellet sandwiched between two thin layers of impermeable biodegradable membrane, with adjustable nanopores permitting only one drug molecule to leave the reservoir at a time (Figure 3). The impermeable polymer layers degrade at a later stage when most of the drug has been released, eliminating the need for device removal.[4]

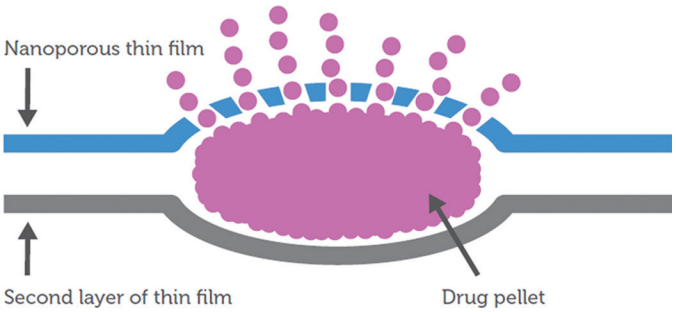

Figure 3. *Nanoporous film device showing the drug pellet sandwiched between two polymer layers, with one side containing nanopores to allow sustained zero-order drug release (adapted with permission from Zordera and ONdrugDelivery Magazine [4]).*

Although all of these implantable systems may achieve sustained release, the release rate cannot be altered if the condition worsens or aborted in the case of serious side effects. This shortcoming has partially been addressed in the port delivery system by ForSight Vision, a scleral plug consisting of a porous container, a semipermeable nonbiodegradable membrane with a refill port (to increase the device's life span), and exit ports to release the drug into the vitreous humor but also to allow for flushing to abort drug delivery. To be able to tune drug delivery on-demand, there has been a paradigm shift from conventional to stimuli-responsive devices over recent years, with such systems also having great potential in the area of ocular drug delivery.[2] Although to date only open-loop systems responsive to light (e.g., ODTx), an electrical stimulus (Figure 4), or a magnetic field (e.g., micro electro mechanical systems [MEMS]) have been explored in the eye,[2] pressure-responsive closed-loop systems may have great potential in the treatment of glaucoma. Moreover, other sensing capabilities combined with a feedback mechanism and stimuli-responsive drug release could offer tailored treatment of posterior segment diseases in the future.

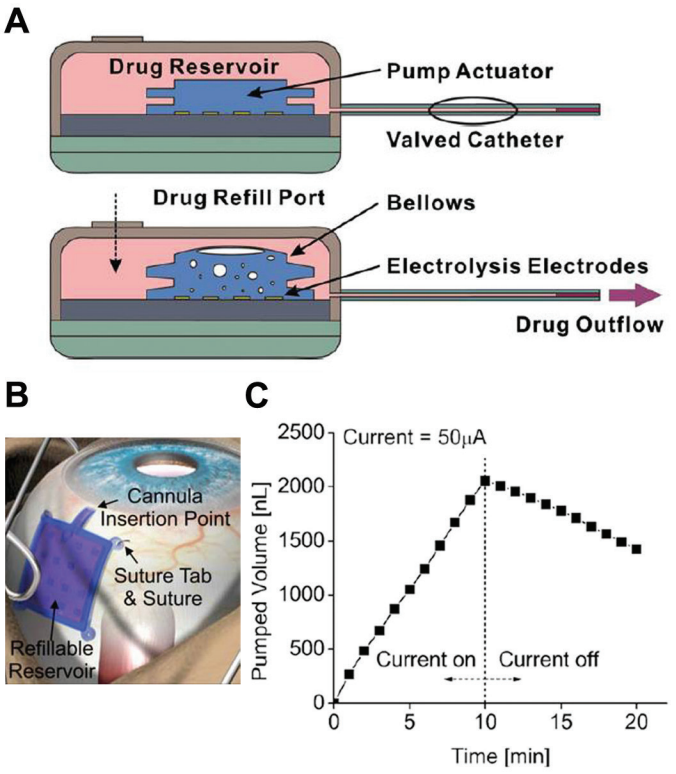

Figure 4. *(A) MEMS-based mini drug pump concept; (B) potential location in the eye; and (C) volume of drug pumped in the presence and absence of an electrical current (© Elsevier, adapted with permission[2]).*

Ocular Drug Delivery – Challenges of Matching New Technologies with Drug Pharmacokinetics

Saturday, July 25, 8:00 a.m. – 5:00 p.m.

Organizers: Ilva Rupenthal, University of Auckland, New Zealand; and Michael O'Rourke, Scotia Vision Consultants, U.S.A.

This workshop will offer scientists both new to and experienced in ocular drug delivery to revisit important ocular barriers and pharmacokinetics to be considered when developing controlled release formulations and to discuss the successes and pitfalls of recent delivery approaches in academia and industry. Clinical requirements, regulatory guidelines and hurdles for new product development, and suitable animal models and preclinical evaluation will also be discussed.

Invited speakers from academia: Arto Urtti (University of Helsinki, Finland), Rocío Herrero-Vanrell, (Universidad de Complutense, Spain), Ilva Rupenthal, (University of Auckland, New Zealand), and Heather Sheardown (McMaster University, Canada).

Invited speakers from industry: Andy Whitlock (Ora, U.S.A.), Brian Levy (Aerie Pharmaceuticals, U.S.A.), Paul Ashton (pSivida, U.S.A.), and Michael O'Rourke, (Scotia Vision Consultants, U.S.A.)

For full workshop details, visit **controlledreleasesociety.org**

Conclusion

A number of innovative drug delivery technologies are currently in the pipeline to treat ocular diseases more efficiently while minimizing side effects, with the majority aiming to sustain drug release over prolonged periods. However, long-term effects of low sustained drug levels especially in the posterior segment are currently unknown, and tunable drug release may be of advantage if the condition improves to avoid unnecessary side effects. The major hurdle with successful development of such tunable implants remains the device size restriction, which in turn reduces the amount of drug loading. Such devices are therefore generally limited to highly potent drugs such as steroids and may become difficult to adapt to macromolecules such as anti-VEGF agents. Moreover, matching these new technologies with drug pharmacokinetics and translating preclinical studies into human clinical trials remains a major challenge. Nevertheless, novel ocular drug delivery technologies offer great market potential, and it is certainly an exciting area to be working in at the present time.

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2015 Nicholas A. Peppas Student Travel Grant Program

Nicholas A. Peppas has been an icon in the field of controlled release through his innovative research, leadership of the Controlled Release Society, and exceptional support of numerous graduate students and postdocs. The CRS Foundation Board has selected Prof. Peppas to be honored at the 2015 annual meeting of the society to be held in Edinburgh, Scotland, on July 26–29 for his achievements and his leadership. The goal is to provide an opportunity for those individuals who have gained personal and professional benefit from his work and leadership to express gratitude.

One of the many legacies attributed to Prof. Peppas involves his vision to enhance the globalization of and student development within CRS through the formation of local chapters. Thus, it is extremely fitting that CRS now wishes to honor him through the funding of student travel awards to allow promising young scientists from these same regional and student CRS chapters to attend the 2015 annual meeting. At this time, we are requesting donations to fund these travel awards and allow the next generation of CRS leaders to meet and learn from Prof. Peppas. Donate now on the CRS website. ■

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Delivery of Therapeutic Bioconjugates: From Polymer Conjugates to Antibody-Drug Conjugates

Roger H. Pak, Pfizer Inc., U.S.A.

Bioconjugation, or the coupling of a biologic through covalent linkage with another molecule to provide some functionality or activity, has increasingly grown in prominence in recent decades. This field began with the maturation of hybridoma and protein expression technologies when tools for improving protein characteristics and analysis were needed. These tools included creation of reagents to label monoclonal antibodies (mAbs) and other proteins with fluorescent molecules, radiometal chelates, and biotin for use in protein and immunoassays. As the creativity and innovation of the scientists in this field took hold, a huge variety of molecular groups (drugs, toxins, photoprobes, polymers, enzymes, ligands, etc.) that could provide useful functionality were covalently conjugated to an equally large variety of proteins or biologic entities (enzymes, nucleic acids, lipids, carbohydrates, small protein constructs, vaccine immunizing agents, biological ligands, etc.).[1] Thus, the field of bioconjugation chemistry began growing dramatically.

The idea of using bioconjugates for therapeutic or diagnostic use also grew at that time. It has been said that bioconjugation chemistry is "medicinal chemistry for biologics." Indeed, polymer conjugates were first developed for therapeutic purposes by attaching synthetic chemical moieties (polyethylene glycol or PEG) on proteins (Figure 1). The initial work by Davis and Abuchowski of conjugating PEG onto protein for alteration and improvement of immunological properties and *in vivo* half-life began the field of PEGylation.[2] The approval of Adagen® (PEGylated adenosine deaminase enzyme) in 1990 for severe combined immunodeficiency disease was the validation of this technology. Approvals for therapeutic PEG-conjugates continued to collect, and by 2013 there were 11 approved PEG conjugates with some products becoming blockbuster medicines (Neulasta, Pegasys, and PEG-intron).

Another type of bioconjugate developed for therapeutic use (in this case against cancer) is the antibody-drug conjugate (ADC, Figure 2). The idea for these ADCs is that a highly cytotoxic drug candidate, which may be too toxic when given directly systemically, could actually ameliorate its safety profile by covalent attachment to a mAb for direct targeting to tumor cells. While attached to the mAb, the cytotoxic molecule is "hidden," but upon internalization into targeted tumor cells, the toxic payload is released in the lysosome and causes cancer cell death. The approval in 2000 of Mylotarg® (anti-CD33 mAb conjugated to calicheamicin payload) for acute myeloid leukemia opened the field for ADCs, and two more cancer-fighting ADCs have since been approved (Adcetris® in 2011 and Kadcyla® in 2013). This field is growing rapidly, and the number of ADCs in clinical trials has increased in recent years.

Other approved or clinical-stage therapeutic bioconjugate formats include radioimmuno-therapeutics/diagnostics (Zevalin®, 2002, mAb conjugated to metal chelator), PEG-conjugated liposome (Doxil®, 1995, doxorubicin in PEGylated liposome), polysaccharide-protein conjugate vaccines (HibTiter®, 1990, and Prevnar®, 2010), fatty acid-peptide

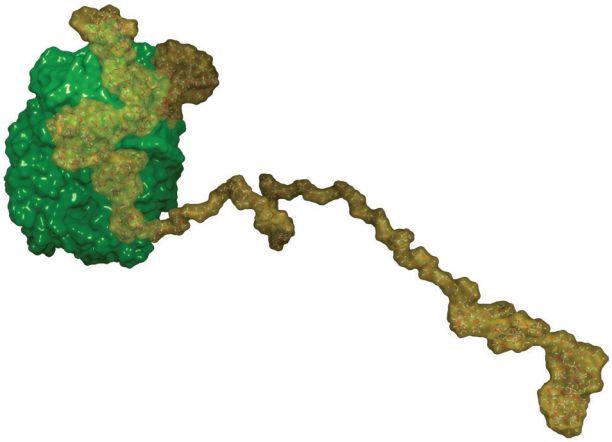

Figure 1. *A structural model of a polymer conjugate based on polyethylene glycol (PEG) polymer conjugated to a small 22 kDa protein scaffold. The surface area colors correspond to protein (green) and PEG (gold slightly transparent surface area and stick figure). Structural model courtesy of Christopher T. Burns.*

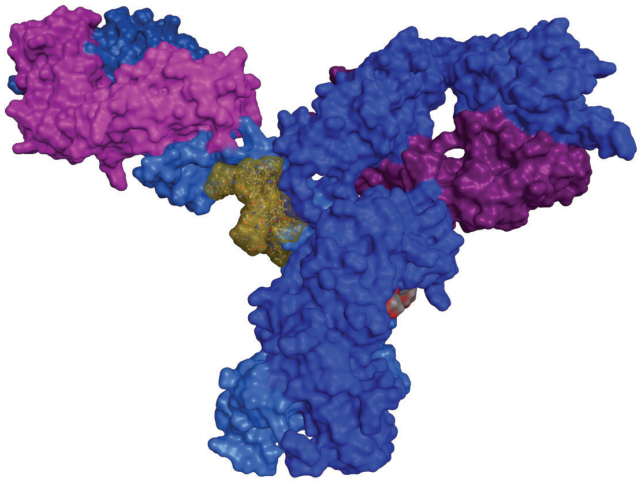

Figure 2. *A structural model of an antibody-drug conjugate based on an IgG_1 scaffold and auristatin payload. The surface area colors correspond to IgG heavy chain (blue and light blue) and IgG light chain (purple and light purple). Note the yellow slightly transparent surface area and stick figure corresponds to the auristatin payload. Structural model courtesy of Christopher T. Burns.*

conjugates (Victoza®, 2013), and small molecule-polymer conjugates (Movantik®, 2014). Many of these bioconjugate formats share the same linker chemistry concerns or development challenges as the polymer conjugates and ADCs.

One common theme for all these bioconjugates is the linker chemistry used to covalently bind the two biomolecules together. Some criteria for linker chemistries to be useful for therapeutic bioconjugation are (1) that the reaction is amenable to mild aqueous conditions, (2) that they react well with and are selective for relevant functional groups on biomolecules (thiols, amines, carboxylic acids, etc.), (3) that any residual linker portions are not genotoxic nor immunogenic, and (4) that they are commercially and economically viable. For polymer conjugates, the majority of linkers are designed to be quite stable and non-releasable. For ADCs, there are both cleavable and non-cleavable linkers used for payload attachment. The rationale for a cleavable linker in an ADC is that upon internalization, the linker will need to release the payload and that a cleavable linker may do that more efficiently. Cleavable linkers are typically degraded through protease or esterase enzymatic activity to provide the free payload, whereas the non-cleavable linker will presumably require proteolytic cleavage of the antibody protein sequence at the site of conjugation to release the toxic payload. The released payload, in this case, is thought to carry a few residual amino acids but to still afford potent cell-killing activity. For both polymer conjugates and ADCs, the linker chemistry is a vital component, and attention to the choice of linker during bioconjugate design is important.

The linker has a role in the chemical and biophysical stability of the bioconjugate. Loss of the PEG moiety due to chemical instability in the linker covalent bond to the biologic could result in shortened drug product shelf life, increase in degradation products with unknown safety profile, and/or shortened *in vivo* half-life extension, possibly resulting in reduced efficacy owing to faster clearance of the active drug species. For an ADC, chemical instability of the linker has more safety concerns. Loss of conjugated cytotoxic payload from an intact ADC, whether during manufacture, storage, or *in vivo* systemic circulation, typically leads to an increase in systemic toxicity. Free toxic payload in circulation has the potential to distribute to numerous normal tissues and cause off-target toxicity. From a biophysical stability standpoint, the choice of linker and extent of conjugation can affect various biophysical attributes of a bioconjugate. For example, the choice of linker chemistry dictates the site of conjugation, which affects both polymer conjugates and ADCs. Location of the PEG polymer has a role in the bioactivity of the protein as well as aggregation propensity. Choice of chemistry, site of conjugation, and number of the linker payloads in ADCs are increasingly found to have an impact on colloidal and thermal stability as well as pharmacokinetics, toxicity, and efficacy.[3,4]

Delivery of Therapeutic Bioconjugates: From Polymer Conjugates to Antibody-Drug Conjugates Workshop

Sunday, July 26, 8:00 a.m. – 12:10 p.m.
Organizer: Roger Pak, Pfizer Inc., U.S.A.

The half-day workshop will explore the topic of therapeutic bioconjugates with a focus on current and future linker chemistries, site-specific conjugation approaches for ADCs, next generation polymer technologies, and biophysical/chemical aspects of polymer conjugates and ADCs. Experts from industry and academia will present the topics and lead the discussion on current progress, challenges, and opportunities.

For full workshop details, visit **controlledreleasesociety.org**

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Seventh Annual CRS Italy Local Chapter Workshop

Paolo Caliceti, University of Padua, Italy

The CRS Italy Local Chapter annual workshop, "Drug Delivery Systems: Pharmacokinetic Challenges and Targeting Strategies," was held in Florence on November 6–8, 2014, with the participation of about 130 delegates.

The participants were welcomed by Paola Mura and Piero Baglioni (University of Florence), who opened the workshop. Bice Conti, president of the CRS Italy Local Chapter, spoke on the goals of CRS and upcoming activities, especially the 2015 CRS Annual Meeting & Exposition in Edinburgh.

Thanks to scientific contributions from some of the most awarded scientists working in the field of drug delivery, the CRS Italy Local Chapter annual meeting confirmed its relevance for the Italian drug delivery community.

In accordance with the excellent outcomes of last year, the workshop was organized to favor open discussion, brainstorming, and information exchange among the participants. Therefore, the meeting was structured into four sessions featuring 18 speakers, who gave 35 minute main lectures followed by 25 minute discussions, which were chaired and directed by panels of scientists.

"Exploring and Struggling with Biological Matter to Open New Avenues for Advanced Drug Delivery" by Stefaan DeSmedt (Ghent University, Belgium) opened the scientific session, giving a view on innovative approaches for the selective delivery of siRNA and miRNA to different tissues based on the bioinspired concept. This lecture warmed up the floor and excellently introduced the theme of the workshop. The second invited lecture, by David Stepensky (Ben Gurion University, Israel), entitled "Approaches for Intracellular Drug Targeting Using Nano-Drug Delivery Systems," described excellently the potential of tumour targeting by surface-decorated PLGA nanoparticles.

The two invited lectures were followed by selected presentations: "Development of Targeted Colloidal Nanoparticles for Breast Cancer Diagnosis and Treatment" by Miriam Colombo (Bicocca University) and "Gentamicin Loaded Nanoparticles for the Local Antibiotic Delivery to Bone" by Rossella Dorati (Pavia University). The speakers presented recent results on colloidal drug delivery systems for active targeting. The presentations were actively discussed and stimulated an interesting brainstorming by the discussant panel and the attendees.

The first two main lectures of the second day were "Passive vs. Active Targeting" by Twan Lammers (RWTH Aachen University, Germany) and "To Target or Not to Target? Hurdles in Targeted Nanomedicine for Preclinical and Clinical Applications" by Dan Peer (Tel Aviv University, Israel), which critically treated the advantages, disadvantages, problems, and opportunities of passive and active targeting. They reported their personal experiences and opinions regarding drug targeting, offering new perspectives to these approaches. The lectures strongly captured the interest of the floor and stimulated a passionate debate among speakers, the discussant panel, and attendees.

The lecture of Roberta Cavalli (University of Turin), "Doxorubicin-Loaded Nanobubbles for Combining Shock Waves and Targeted Chemotherapy," reported an original approach for tumour targeting in which physical stimuli and internal triggering are combined to yield efficient tumor targeting.

The relevance of the physical design of drug delivery systems to achieve tumour targeting was well illustrated by Paolo Decuzzi (Methodist Hospital of Houston, U.S.A.) with his lecture "Discoidal Polymeric Nanoconstructs with Unprecedented Longevity in Blood and Tumor Accumulation." According to a passive targeting approach, he showed that particles can be geometrically and dimensionally designed to yield tumour accumulation.

The key role played by materials constituting colloidal drug delivery systems was treated by Yvonne Perrie (Aston University, U.K.) in her talk "Is There a Role for Controlled Release in Vaccine Formulation?" She discussed the importance of using liposomes with tailored composition to optimize the delivery of vaccines. Her convincing talk gave new perspectives in the design and development of vaccines.

Giuseppe De Rosa (Federico II University of Naples) presented on "Self-assembling Nanoparticles for Drug Delivery: Advantages, Potentialities and Issues," which completed the broad overview on colloidal systems for tissue targeting.

Attendees listen attentively during the plenary session.

An energetic discussion with invited speakers Twan Lammers (left) and Dan Peer (right).

The last session was mainly dedicated to the delivery of macromolecules, a hot topic in pharmaceutical development. This session featured two outstanding scientists: Randall Mrsny (Bath University, U.K.), and Enrico Mastrobattista (Utrecht University, the Netherlands). Mrsny's "Understanding and Developing the Science Behind Oral Protein and Peptide Delivery" was a great occasion for participants to learn about mechanisms, issues, and potential approaches in the delivery of peptide and protein drugs though mucosae, namely, in oral delivery. Enrico Mastrobattista gave a fascinating talk, "Polymer and Peptide-Based Vectors for Gene Delivery," in which he highlighted the importance of proper design for the delivery of oligonucleotides. In his talk, he highlighted the role played by biological barriers that impede the delivery of oligonucleotides and possible solutions from successful experiments with peptide-based nanovectors.

Sara Nicoli (Parma University) presented "Iontophoretic Delivery of Macromolecules Across the Sclera," and Aurèlie Schoubben (Perugia University) presented "Inhalation Therapy for Pulmonary Infections," which reported their studies on innovative approaches to overcome the biological barriers.

Aside from strictly scientific research-based lectures, the workshop featured speakers who gave an industrial vision of the development of innovative nanopharmaceuticals. Shadi Farhangrazi (Denver University, U.S.A.) gave a talk that stimulated an active debate: "Success by Design: What Do We Want the Future of Nanomedicine (or Medicine) to Look Like?" Kevin W. Burton (Evonik, U.S.A.) presented "Formulation Development of Complex Parenteral Products," which highlighted the problems and solutions that underlie the development of colloidal systems with supramolecular architectures. Finally, Frédérique Bordes-Picard (Capsugel, France) introduced the relevance of the patient-centric approach in the design of novel pharmaceuticals in "Patient Centric Focus Design: Changing the Development Paradigm."

Delegates highly appreciated the contribution of speakers with experience in industrial aspects of drug delivery. The lectures emphasized the final goal of research in drug delivery, namely, to provide effective and exploitable solutions for public health. A number of considerations must be kept in mind when a novel system is designed, including industrial development and marketing.

The workshop included a poster session with 62 contributions. Posters were orally presented with three-minute snap talks. Two posters received awards: Michela Barattin (Padua University), "Liposomes with pH-Controlled Cell Penetrating Activity or Site-Specific Anticancer Drug Delivery," and Alice Melocchi (University of Milano), "3D-Printing: Application Potential for the Manufacturing of Drug Delivery Systems in the Form of Capsular Devices." The first award was selected by a committee composed of the invited speakers, while the second prize was selected by the vote of all delegates.

The workshop closed with concluding remarks by Yvonne Perrie, Anna Rita Billia (University of Florence), and Moein Moghimi (University of Copenhagen).

The workshop program was a great success, and participants greatly appreciated the contributions of invited speakers because they didn't limit themselves to presenting their research but were actively involved in the critical open-minded discussion, which opened novel viewpoints on research in nanopharmaceuticals.

Social activities included a welcome cocktail and a social dinner attended by all delegates. These important events provided networking opportunities.

The workshop was supported by CRS and generously sponsored by QI Technologies, Evonik, Capsugel, Alfatest-Malvern, Buchi, Menarini, PANanalytical, Anton-Paar, TA Instrument, Bio-Targets, LS-analytica, Bio-Instruments, and ML Master Lab. The sponsors provided support for the participation of several young scientists.

All abstracts have been uploaded to the website of the CRS Italy Local Chapter. ■

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In the News

Compiled by Steven Giannos, Independent Consultant

February

TWi Pharmaceuticals Announces That It Will Sell Its Products in the U.S. Market, Originally Planned to Be Sold by Teva, Through Its Wholly Owned Subsidiary, TWi Pharmaceuticals USA

PRNewswire: February 23, 2015 – TAIPEI, Taiwan – TWi Pharmaceuticals, Inc. ("TWi") (4180: Taiwan) today announced that TWi and Teva Pharmaceuticals ("Teva") have reached an agreement that will transfer the U.S. sales and distribution rights of TWi's generic versions of Megace® ES (megestrol acetate oral suspension, 625 mg/5 mL) and Lidoderm® (lidocaine patch, 5%) from Teva to TWi. TWi will distribute both products through its wholly owned subsidiary, TWi Pharmaceuticals USA.

TWi has assembled a sales and distribution team in the United States and plans to launch several products in the United States under TWi's label this year.

"We are excited that we are going to sell our products under the TWi label, and TWi will be able to enjoy all the profits derived from the products. We are optimistic about the change, which is consistent with the company strategy," said Dr. Calvin Chen, president of TWi Pharmaceuticals, Inc.

TWi Pharmaceuticals, Inc., is a leading specialty pharmaceutical company based in Taipei, Taiwan, focusing on the development of high barrier generic prescription products ranging from oral controlled release dosage form to novel drug delivery systems including the utilization of nanoparticles, transdermal, and polymeric oral delivery systems. Leveraging its internal research and development capabilities, together with operational flexibility, process development, manufacturing, and regulatory expertise, TWi Pharmaceuticals concentrates on products and technologies that present significant barriers to entry or offer Paragraph IV first-to-file or first-to-market opportunities in the United States. For more information on TWi Pharmaceuticals, please visit www.twipharma.com.

Follicept™ Hair Growth Gel Set for Launch in 2015 by UF Transdermal Delivery Startup

Business Wire: February 23, 2015 – GAINESVILLE, FL, U.S.A. – With the patent expiration of Rogaine® and Propecia®, there is no longer a clear market leader in the $3.5 billion/year hair growth industry. Follicept™, developed by University of Florida spinoff Prometheon Pharma, is poised to fill that role in 2015 and challenge mediocre and often expensive drug, laser, and surgical treatments.

Follicept is considered a cosmetic, delivering extremely small yet effective doses of IGF-1, which naturally blocks the effects of testosterone on hair follicles. This creates a positive feedback loop, so a single dose of IGF-1 will remain active for many hair follicle life cycles. It avoids the "shedding" observed with Rogaine®, a common complaint of its users.

"Compounding the problem of spotty performance, current products for 'male pattern baldness' ignore up to 40% of those with androgenetic alopecia who are women," said Dr. Stephen Hsu, CEO of Prometheon Pharma and inventor of its new Follicept hair growth gel. Prometheon is also known for its Topicon™ transdermal drug delivery technology and flagship needle-free insulin TruePatch™ under development. Follicept is the first in Prometheon's dermatology product line. "People of all ages and genders face this cosmetic concern that carries with it a heavy psychological toll and no effective long-term solution," Hsu added.

Rogaine® (J&J's 5% topical minoxidil, first discovered in 1978) and Propecia® (Merck's finasteride testosterone-inhibitor pill) have long been in use to treat androgenetic alopecia, most commonly a genetic trait. However, Rogaine® is not a long-term solution and Propecia® is associated with impotence. Not surprisingly, only ~1% of 56 million men and women with this condition actually use these products, yet this still drives a remarkably profitable and growing multi-billion dollar industry in the United States.

"There have been few significant advancements in nearly 40 years because industry couldn't deliver the known ideal compound, IGF-1, safely and locally across the skin. We are excited to announce that with Follicept, the wait is finally over," declared Hsu.

Prometheon Pharma is a biotechnology company housed in the globally #1-ranked Sid Martin Biotech Incubator at the University of Florida. Prometheon is dedicated to increasing patient compliance and access as well as reducing healthcare costs with its platform needle-free transdermal, low-refrigeration patches for large peptide and protein drugs.

Otic Pharma Announces Encouraging Feedback from a Pre-IND Meeting with the Food and Drug Administration (FDA)

Business Wire: February 23, 2015 – REHOVOT, Israel – Otic Pharma, a privately held biopharmaceutical company focused on the development of innovative, localized, aerosol foam-based products for ear, nose, and throat (ENT) disorders, announces encouraging feedback from a pre-IND meeting held recently with the FDA concerning the clinical development plan of its lead investigational new drug product, FoamOtic Externa (0.3% ciprofloxacin). FoamOtic Externa is a single-agent, steroid-free

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product, which was studied in a phase 2 clinical trial with 220 minor and adult patients with acute otitis externa (AOE). The agency agrees that the 505(b)(2) new drug application regulatory pathway is appropriate for the submission of the FoamOtic Externa product. FDA agrees that a single placebo-controlled phase 3 clinical trial might be potentially adequate, pending review of the total information submitted in the NDA.

Otic Pharma is developing FoamOtic Externa (0.3% ciprofloxacin), a novel aerosol foam formulation of ciprofloxacin for ototopical administration in the treatment of AOE. The purpose of the pre-IND meeting was to obtain the agency's comments and guidance regarding the clinical development program in support of NDA filing.

"We are very pleased with the positive feedback from the agency with regard to the development plan of FoamOtic Externa. Based on the responses received from the agency, we will be initiating a U.S.-based phase 3 clinical trial with FoamOtic Externa during 2015," said Orna Palgi, Ph.D., executive vice president of Otic Pharma.

The planned clinical trial is a randomized, multicenter, placebo-controlled, double-blind, phase 3, enrolling approximately 400 patients, 6 months of age and older. Study endpoints include cure rate, pathogen eradication rate, time-to-end of pain, and safety profile of the drug.

FoamOtic Externa is an investigational proprietary, foam-based, extended-release formulation of ciprofloxacin antibiotic, which has been designated for self-applied once-daily administration to potentially treat AOE.

The FoamOtic platform attempts to address the inherent limitations of ear drops. For example, the foam should provide good coverage of the infected area; it does not drip out of the ear, providing continuous release of the drug.

The primary indication studied for FoamOtic is for the potential treatment of AOE in minor and adult patients.

Otic Pharma, established in 2008, is a clinical-stage company with a pipeline of products for the treatment of ENT disorders. The products are based on FoamOtic, a proprietary foam-based drug delivery system providing sustained exposure of drugs. Otic Pharma has three additional product candidates in preclinical development. FoamOtic Externa completed a phase 2 clinical trial in minor and adult patients with AOE and is transitioning to initiate a U.S.-based phase 3 pivotal trial to support a potential NDA submission in 2016.

Ferring Pharmaceuticals Acquires Novel Drug Delivery Technology from CTCBIO Inc.

Business Wire: February 23, 2015 – SAINT PREX, Switzerland – Ferring Pharmaceuticals announced today that it has signed an agreement with CTCBIO Inc. of Seoul, South Korea, to acquire rights to a novel oral drug delivery technology. Ferring's success in developing oral formulations for peptide drugs including the world's first orally active peptide, desmopressin (MINIRIN®) and the fast dissolving lyophilisate (MINIRIN® MELT), is well known. CTCBIO is a growing specialist company that has developed successful manufacturing technologies for more than 30 different drugs, including treatments for dementia and asthma.

"Ferring has been a pioneer in the development of novel oral drug delivery technologies," says Per Falk, M.D., Ph.D., executive vice president and chief scientific officer at Ferring, "Our portfolio of peptide therapeutics make us an attractive partner for specialty technology-based companies like CTCBIO to collaborate on new approaches for oral drug delivery of peptides and proteins."

"Keeping the active pharmaceutical ingredient stable and secure is critical," explained Dr. Jeon Hongryeol, vice president of CTCBIO. "This technology makes this possible and is particularly useful for hydrophilic macromolecules like peptides and proteins while offering the advantage of oral administration."

Under the agreement involving an undisclosed up-front payment, milestone, and royalty terms, the two companies will collaborate to develop prototype formulations for *in vitro* and *in vivo* testing and the subsequent up-scaling required to manufacture the technology to meet worldwide good manufacturing practice (GMP) requirements.

EastGate Biotech Engages Distribution Company for Its Nutraceutical Products for Canadian Market

PRNewswire: February 23, 2015 – SALT LAKE CITY, UT, U.S.A. and TORONTO, Canada – EastGate Biotech Corp. (OTCBB: ETBI), an emerging pharmaceutical company aimed at utilizing drug delivery innovations in the development of improved novel formulations and alternative dosage forms of existing biologically active molecules engages Preferred Nutrition (www.pno.ca) to distribute the company's nutraceutical and natural consumer products across Canada.

Preferred Nutrition Inc. is a Canadian premier distribution company founded in 2002. It primarily distributes to approximately 1,200 health food stores across Canada. It represents five top product lines for a total of 78 products in the vitamin and supplement category.

Preferred Nutrition will initially start marketing E-drops, which is a natural and herbal alternative that assists to rid the body of UTI infections painlessly and effectively without side effects of synthetic drugs. Preferred Nutrition is also reviewing the marketing of other EastGate products, such as vitamin D3 drops, Glucora, and so on.

Information on EastGate's natural product line can be found at www.nano-essentials.com. Previously, the company announced a distributor for its nutraceutical product line including E-drops in the United States under its own private label.

"We are pleased to have established a distribution relationship with Preferred Nutrition Inc. as it validates the marketplace's demand for new and innovative products such as those delivered through EastGate's proprietary sub-micron self-nanoemulsifying platform technology," said Anna Gluskin, EastGate's CEO. "E-drops, which is the first product that will be launched by Preferred Nutrition, is a unique product in its classification to aid in the natural elimination of UTI infections, and the company's distribution network will provide increased visibility to consumers in the growing natural product marketplace," continued Gluskin.

Richter and Evestra Enter into Collaboration Agreement

Business Wire: February 19, 2015 – BUDAPEST, Hungary, and SAN ANTONIO, TX, U.S.A. – Gedeon Richter Plc. and Evestra Inc. today announced that they have signed a collaboration agreement in which Richter is providing a US$5 million convertible loan to Evestra. The funds will empower Evestra to accelerate the development of its innovative women's health product pipeline into clinical stages.

Under the terms of the agreement, after three years Richter has an option to decide whether the loan is to be reimbursed, including earned interest, or converted into an equity stake in Evestra.

Gedeon Richter Plc. (www.richter.hu), headquartered in Budapest, Hungary, is a major pharmaceutical company in Central Eastern Europe, with an expanding direct presence in Western Europe. Richter's consolidated sales were approximately EUR 1.1 billion (US$1.5 billion), while its market capitalization amounted to EUR 2.1 billion (US$2.5 billion) in 2014. The product portfolio of Richter covers almost all important therapeutic areas, including gynecology, the central nervous system, and cardiovascular areas. Having the largest R&D unit in Central Eastern Europe, Richter's original research activity focuses on CNS disorders. With its widely acknowledged steroid chemistry expertise, Richter is a significant player in the female healthcare field worldwide. Richter is also active in biosimilar product development.

Evestra, Inc. (www.evestra.com) is a San Antonio, Texas-based biopharmaceutical company engaged in the development of innovative women's healthcare products. Evestra's products are based on two platform technologies, medicinal chemistry and vaginal drug delivery technology, and address unmet medical needs in women's health arenas.

pSivida Announces U.S. Shipments of ILUVIEN® for DME to Start February 23

Business Wire: February 17, 2015 – WATERTOWN, MA, U.S.A. – pSivida Corp. (NASDAQ: PSDV) (ASX: PVA), a leader in the development of sustained release drug delivery products for treating eye diseases, today announced that initial nationwide shipments of ILUVIEN® for diabetic macular edema (DME) are scheduled to begin in the United States on February 23, 2015.

A live webinar launch event designed for eye care professionals is scheduled for March 2, 2015, at 8:30 p.m. EST by pSivida's licensee, Alimera Sciences. On the webinar, eight retinal specialists and one glaucoma specialist from around the country will share their experiences with ILUVIEN, including videos of ILUVIEN injections, and participate in a live question and answer session to share information about ILUVIEN. Executives from Alimera will also be available to address product distribution and reimbursement questions. The one-hour webinar will be accessible online, and those interested in registering for the webinar may do so in advance at www.iluvien.com.

"We are very pleased that shipments of ILUVIEN will begin next week," said Dr. Paul Ashton, president and CEO of pSivida. "ILUVIEN represents an important treatment option for many diabetics who are losing vision due to DME." pSivida is entitled to 20% of net profits on the sales of ILUVIEN on a country-by-country, quarter-by-quarter basis.

ILUVIEN is an injectable, sustained release micro-insert approved in the United States to treat DME patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. ILUVIEN delivers the steroid flucinolone acetonide in submicrogram levels on a continuous basis for a period of 36 months. It is expected that ILUVIEN will be reimbursed in the United States for its FDA indication. Alimera has set up a reimbursement and patient assistance program to support practices and patients with respect to ILUVIEN.

pSivida Corp. (www.psivida.com), headquartered in Watertown, Massachusetts, develops tiny sustained-release products designed to deliver drugs and biologics at a controlled and steady rate for weeks, months, or years. Using its core technology platforms, Durasert™ and Tethadur™, the company is focused on treatment of chronic diseases of the back of the eye and is also exploring applications outside ophthalmology. The company's lead product candidate, Medidur™, uses the same injectable, sustained release micro-insert as pSivida's lead licensed product, ILUVIEN® for the treatment of DME. ILUVIEN has been approved in the United States, is marketed in the United Kingdom, Germany, and Portugal, and has or is pending marketing authorization in 14 other EU countries. pSivida's other licensed product, Retisert®, an implant that treats posterior uveitis, is sold in the United States. pSivida's preclinical research is focused on ocular and systemic delivery of biologics and drugs to treat wet and dry age-related macular degeneration, glaucoma, osteoarthritis, and other diseases.

Kinex Pharmaceuticals Licenses Patents from Hong Kong Polytechnic University

PSNewswire: February 13, 2015 – HONG KONG – Kinex Pharmaceuticals today announced the exclusive licensing of global rights of three patents from the Hong Kong Polytechnic

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University and McGill University. These three patents covered the inventions by Prof. Larry Chow and Prof. William Chan, including novel new chemical compounds that have nanomolar potency against a molecular target named breast cancer resistance protein (BCRP). BCRP is a protein pump known to pump drugs, including anticancer drugs, from cancer cells that can lead to drug resistance, and also to pump drugs back into gastrointestinal tract, preventing some useful drugs from being delivered to their target.

The development of this technology, if successful, will expand the current Kinex oral drug absorption development platform. That platform currently includes the inhibition of P-glycoprotein that Kinex licensed from Hanmi in 2011. The lead molecule, HM30181A, has been shown in clinical studies to enhance the absorption of anticancer drugs including paclitaxel and irinotecan into orally available drugs. The lead program, Oraxol (an oral form of paclitaxel), has demonstrated clinical efficacy and an excellent safety profile in patient studies. Kinex is also actively developing other proprietary oral drug delivery platforms. The addition of another oral absorption delivery technology platform will further strengthen Kinex's arsenal of converting greater classes of intravenous drugs into oral versions.

The terms of this exclusive license include upfront payments, milestones, and royalties. Kinex is also committing to support research programs in Prof. Larry Chow's laboratory to further develop this platform collaboratively with Kinex.

Johnson Y. N. Lau, MBBS, MD, FRCP, chairman and CEO of Kinex Pharmaceuticals, stated, "The research of Prof. Larry Chow complements Kinex's drug development efforts. Kinex is a leader in the development of proprietary oral drug formulation and dosing for some of the important anticancer drugs including paclitaxel and irinotecan, which currently have to be given intravenously. Oral versions of these drugs can be more efficacious and have fewer side effects for the patients. The discovery of lead molecules against another target such as BCRP that can enhance oral drug absorption by Prof. Larry Chow and William Chan, if successfully developed clinically, will add to the arsenal of tools for Kinex. We are excited to collaborate with Prof. Larry Chow to further develop this drug delivery platform and to convert more current intravenous drugs into oral form."

Flint Besecker, COO of Kinex, said, "We have learned in the clinic that converting existing intravenous drugs into oral forms opens the door to a wide array of proprietary formulation and titrated patient dosing regimens that are not possible through IV delivery systems. Oral forms of dosing allow the patients to be exposed over a longer period of time to the active pharmaceutical ingredients with less adverse side effects. This drug development strategy has less inherent risks, and we are excited at the possibilities to make a difference in helping more patients. Such an effort, if successful, will have the potential to impact healthcare delivery globally and substantially."

Larry Chow, Ph.D., professor and associate head of the Department of Applied Biology and Chemical Technology, commented, "I was impressed by Kinex in their ability to work with Hanmi Pharmaceuticals to advance the research program using a P-glycoprotein inhibitor to enhance the oral absorption of important drugs like paclitaxel and irinotecan and demonstrate its clinical utility. We are delighted that they will partner with us to help optimize our lead compound into a potentially useful molecule in the clinic for other drugs that are not absorbed orally because of this biologic pump system. Working with this wonderful group of industry veterans will allow us to tap into their expertise and to develop this platform further. I am excited with this collaboration."

Nick Yang, executive vice president of the Hong Kong Polytechnic University, stated, "To be able to establish successful collaborations between academia and industry is the mission of our university in transferring novel discoveries into useful applications that can help the community and serve the society. We are confident that the collaboration between PolyU and Kinex will open a new chapter for cancer drug development, bringing new hope to cancer patients globally and taking us one step closer to a revolution in cancer treatments."

Actavis to Divest Pharmatech to TPG

PRNewswire: February 13, 2015 – DUBLIN, Ireland, and FORT WORTH, TX, U.S.A. – Actavis plc (NYSE: ACT) and TPG, the global private investment firm, today announced that they have entered into definitive agreements, under which Actavis will divest to TPG the business currently known as Aptalis Pharmaceutical Technologies (Pharmatech)—a pharmaceutical outsourcing and R&D business within Actavis's subsidiary Aptalis operating in the United States, Canada, and Europe (where the transaction is, in certain jurisdictions, still subject to local regulations, discussions, and clearances). No other Aptalis businesses or products are included in the transaction. No financial terms were disclosed.

Pharmatech is a leader in pharmaceutical R&D and manufacturing, with specialized capabilities in areas such as taste-masking and customized drug release and the ability to support projects from formulation through scale-up and commercial-scale manufacturing. John Fraher, current president of Aptalis Pharmaceutical Technologies, will become CEO of the new standalone company, and will be joined by others from his management team. The business will continue to operate integrated R&D and manufacturing facilities in North America and Europe.

"Our decision to divest the Pharmatech business is consistent with our strategic commitment to build leadership positions in our core areas of strength," said Robert Stewart, chief operating officer of Actavis. "It will enable our industry-leading global operations team to sharpen their focus on supporting our existing global supply chain and on preparing for the expansion of our manufacturing network with the addition of the Allergan facilities following the close of the acquisition later this year. The Pharmatech team has

done an exceptional job in meeting its objectives, and I would like to thank them for the tremendous work they have done for Actavis. The decision to divest Pharmatech will have no impact on our commitment to investing in and developing our industry-leading Medis third-party business."

"We see great demand in the market for Pharmatech's drug delivery and R&D expertise, and by launching this platform, we hope to continue to support the growth and innovation of pharmaceutical companies, both through the development of *de novo* products, novel value-added formulations, and targeted generic products," said John Schilling of TPG.

By acquiring Pharmatech, TPG intends to use the company as a platform to enter into new partnerships and make additional acquisitions to grow the business. TPG's healthcare practice has invested approximately $6 billion in equity since 2007, and the firm has executed more than 20 carve-outs from major corporations since its founding.

"We're excited to renew our partnership with TPG and believe the firm's experience in the pharma industry, combined with their past successes in establishing market-leaders from carve-outs, positions us well to build a new, successful platform," said John Fraher, president of Aptalis Pharmaceutical Technologies.

The transaction is expected to close by mid-2015 and is subject to customary closing conditions and regulatory approvals.

NanoSmart Receives FDA Orphan Drug Designation for ANA-Conjugated Liposomal Doxorubicin for the Treatment of Ewing's Sarcoma

PRNewswire: February 11, 2015 – LAGUNA HILLS, CA, U.S.A. – NanoSmart® Pharmaceuticals, Inc., a private pharmaceutical company developing nanoparticle drug delivery platforms, has received orphan drug designation from the Food and Drug Administration (FDA) for one of its lead candidates, antinuclear antibody (ANA) conjugated liposomal doxorubicin. The drug product is initially intended to treat Ewing's sarcoma, a rare type of cancer that develops in or around children's bones, with potential expansion into other indications.

NanoSmart is developing an improved, ANA-targeted, liposomal formulation of doxorubicin that focuses drug delivery at the tumor site. Nonclinical testing of NanoSmart's formulation has been promising, revealing its potential to improve the safety and efficacy of liposomal doxorubicin. Because ANA conjugation enables the drug to bind to areas of necrosis that are present in solid tumors, NanoSmart anticipates expanding into additional pediatric indications.

"We are very pleased that the FDA has approved our request for orphan drug designation," explains Dr. James Smith, president of NanoSmart Pharmaceuticals, "This is an important regulatory milestone and the incentives enabled by this designation will allow us to continue with a very cost-effective commercialization strategy."

The FDA grants orphan status to drug therapies for rare diseases that affect less than 200,000 persons in the United States, and to sponsors that provide a plausible hypothesis that their drug formulation may be clinically superior to the same drug that is already approved for the same orphan indication. Sponsor companies qualify for certain development incentives, such as FDA fee waivers, substantial tax credits, access to grant funding for clinical studies, and potential for a period of market exclusivity upon approval.

NanoSmart Pharmaceuticals, Inc., is a privately held company engaged in developing novel methods to treat cancer and other diseases. The company is focused on using its patented tumor targeting antibodies to develop a variety of biopharmaceuticals to treat many different types of cancer. This press release may contain forward-looking statements that involve risks and uncertainties associated with product development and other business operations. NanoSmart's drug compounds are not approved by the FDA or other comparable regulatory agency. There can be no assurance that these forward-looking statements will prove to be accurate, and they should not be regarded as a representation that the objectives and plans will be achieved.

Relmada Therapeutics Selects MepiGel Formulations to Advance into Clinical Studies

PRNewswire: February 4, 2015 – NEW YORK, NY, U.S.A. – Relmada Therapeutics, Inc. (OTCQB: RLMD), a clinical-stage company developing novel therapies for the treatment of chronic pain, announced today that the company has selected the formulations to be advanced into clinical studies for MepiGel, the company's topical dosage form of the local anesthetic mepivacaine being studied for the treatment of neuropathic pain.

"MepiGel is designed to offer a number of advantages over existing patch forms of treatment, including greater skin penetration and retention along with application advantages in areas of poor adhesion," stated Sergio Traversa, chief executive officer of Relmada Therapeutics. "We believe these are important product distinctions and support our plans to work toward the initiation of clinical studies."

The MepiGel formulations were chosen after the evaluation of results from *in vitro* and *ex vivo* studies comparing various topical prototypes of mepivacaine that were conducted by MedPharm Ltd., a specialist formulation development company recognized internationally for its expertise in topical and transdermal products. Relmada is planning single and multiple dose phase I studies in healthy subjects with the selected MepiGel formulations later this year. The data from these studies will inform the design of a subsequent phase 2 proof of concept study in patients suffering from neuropathic pain.

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Aurinia Pharmaceuticals Announces Recently Granted Nanomicellar Formulation Patents in Japan and China for Topical Ophthalmic Administration of Voclosporin

Business Wire: February 3, 2015 – VICTORIA, BC, Canada – Aurinia Pharmaceuticals Inc. (the "company") (NASDAQ: AUPH / TSX: AUP) today announced that the company has recently been granted patents by the Japanese and Chinese patent offices for its nanomicellar formulation of voclosporin. These are in addition to multiple other patents that have been issued and granted in the United States, Mexico, and Australia for ophthalmic administration of voclosporin. Further patent prosecution in other regions is ongoing.

"We are very excited about the potential for ocular administration of voclosporin utilizing this unique nanomicellar drug delivery technology. This formulation enables high concentrations of voclosporin to be put into solution for local delivery to the ocular surface" said Stephen Zaruby, president and CEO of Aurinia Pharmaceuticals Inc.

Completed preclinical and phase I studies using this nanomicellar technology in combination with voclosporin have shown encouraging results in terms of delivery of active drug to target tissues. In addition, this nanomicellar formulation of voclosporin has the potential to improve dosing frequency and tolerability.

"Ophthalmic nanomicellar voclosporin has the potential to compete in the billion dollar prescription dry eye market currently dominated by Restasis® (cyclosporin ophthalmic emulsion 0.05%) with what appears to be a very competitive product profile" said Neil Solomons, M.D., chief medical officer of Aurinia Pharmaceuticals Inc.

"The company plans to review its strategic options as it relates to this ophthalmic formulation of voclosporin and the nanomicellar delivery technology including but not limited to outlicensing or divestiture while at the same time remaining focused on our lupus nephritis program," said Mr. Zaruby.

Aurinia is a clinical stage pharmaceutical company focused on the global nephrology market. It is currently enrolling patients in its phase 2b clinical trial to evaluate the efficacy of its drug, voclosporin, as a treatment for lupus nephritis (LN). LN is an inflammation of the kidneys that, if inadequately treated, can lead to end-stage renal disease, making LN a serious and potentially life-threatening condition.

Voclosporin is a novel and potentially best-in-class calcineurin inhibitor (CNI) with extensive clinical data in over 2,600 patients in other indications. Voclosporin is made by a modification of a single amino acid of the cyclosporine molecule (a CNI approved for use in transplant patients since 1983). This modification results in a more predictable pharmacokinetic and pharmacodynamic relationship, an increase in potency versus cyclosporine, an altered metabolic profile, and potential for flat dosing.

Aurinia also has development and commercialization partners in Canada, Israel, South Africa, and Greater China. Visit www.auriniapharma.com, www.sedar.com, and www.sec.gov for more information.

Restasis® (cyclosporin ophthalmic emulsion 0.05%) was approved by the U.S. Food and Drug Administration in December 2002 to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with chronic dry eye. Restasis® is a registered trademark of Allergan Inc.

SinuSys to Support Clinical Study of New Steroid-Eluting Spacer Designed to Improve Sinus Surgery Outcomes

Business Wire: February 3, 2015 – PALO ALTO, CA, U.S.A. – SinuSys Corp., an innovative sinus health company, today announced commencement of a new clinical trial studying its proprietary drug-eluting spacer infused with steroids for use following functional endoscopic sinus surgery (FESS). The device is designed to steadily and predictably deliver the drug over a seven-day period before removal.

The double-blind randomized trial will study the investigational SinuSys technology in 48 patients with chronic rhinosinusitis. The study will compare the SinuSys technology with the current standard of care (silastic spacers) and will be evaluated at 7, 35, and 90 days. The trial is sponsored by St. Paul's Sinus Centre in British Columbia, with Amin Javer, MD FRCSC FARS, director of the St. Paul's Sinus Centre and assistant clinical professor at the University of British Columbia, serving as principal investigator.

Primary endpoints of the trial are a reduction in postoperative interventions and use of steroids. Secondary endpoints include the incidence of scarring, inflammation, and other outcomes measurements, including SNOT (Sino-Nasal Outcome Test) 22, and Philpott–Javer, and Lund–Kennedy scores.

"There is a clinical need for a spacer that delivers a therapeutic agent predictably over a longer period of time than is currently available. This new technology shows promise in doing that, with the ultimate goal of improving patient outcomes after FESS," said Dr. Javer.

The SinuSys spacer is made of a rate-controlled membrane designed to protect the steroid within from fluids in the sinus environment, eliminating the bolus dose of steroid often seen with polymer or biofilm. The device has the potential to mitigate systemic use of steroids, which has been shown to be a health risk for patients.

"While this study is adjunctive to surgery, the technology offers the potential to serve as a stand-alone procedure for virtually any patient requiring steroids," said SinuSys chief executive officer Thomas Schreck. "This drug-infused device is designed to amplify the benefits of FESS and was developed based on the company's

many years of institutional experience working with drug delivery technology."

Scarring in the sinus—or synechiae formation—is the most common complication after surgery, occurring in 4–35% of the more than five million FESS cases performed annually in the United States. Traditional spacers are only partially successful in promoting healing and preventing scarring, while drug-eluting stents deliver steroids in a bolus dose that does not continue through the healing process. Scarring has been shown to impair ventilation and FESS outcomes. A U.S. pivotal trial is planned following the conclusion of the trial.

SinuSys Corp. (www.sinusys.com) strives to improve the health of patients worldwide through the development and commercialization of the Restora™ drug delivery technology, the Vent-Os™ sinus dilation system, and other osmotic and rate-controlled therapies for serious ear, nose, and throat conditions. The company's proprietary technologies are designed to be atraumatic, tissue-sparing, and easy to use, potentially enabling clinicians to intervene at earlier stages of sinus disease.

January

Microneedles Breakthrough Brings 3M One Step Closer to Introducing New Alternative Drug Delivery Method

Business Wire: January 28, 2015 – ST. PAUL, MN, U.S.A. – Getting an injection at the doctor's office typically does not rank high on many people's wish list. Thanks to 3M scientists' know-how, the day is getting closer when patients may be receiving their prescription medications at home via microscopic needles. Pharmaceutical and biotechnology companies can now partner with 3M on development and conducting clinical trials using its 3M™ Hollow Microstructured Transdermal System (hMTS). Patient-friendly and easy to use, 3M hMTS is designed to open new opportunities for pharmaceutical companies and patients.

The device's availability for clinical trials comes after conducting a number of studies and design verification tests. Based on 3M microreplication technology, pharmaceutical and biotech companies can take advantage of this patient-friendly hollow microneedle device for difficult-to-deliver biologics.

To reach this current stage of clinical readiness with the hMTS device, 3M has undertaken a rigorous process, including finalizing the device design, manufacturing critical components from medical grade materials, establishing GMP array manufacturing and device assembly, as well as filing documentation with FDA.

3M conducted a human tolerability study with the goal of selecting the appropriate microneedle array for use in clinical studies. The outcome of this study found very good delivery times for 2 mL (less than 2 minutes on average). These results provide foundational data in assessing the safety of the device. Clinical supplies are now available for assessment in potential development partners' trials.

"From the foundation laid by our recent human study, we are excited to extend our hollow microneedle device and expertise to companies who are ready for clinical studies. Pharma companies can now evaluate 3M hMTS in their clinical trials as a delivery system for a new drug product or a product line extension," said Ingrid Blair, vice president, business and marketing, 3M Drug Delivery Systems. "Keeping patient preference top of mind is key, and with this new system, pharmaceutical companies have more options to satisfy patients."

"3M™ Hollow Microstructured Transdermal System continues to demonstrate a number of unique benefits, including reproducible intradermal delivery, a proven ability to deliver formulations up to 2 mL with various viscosities, and API-dependent PK profile benefits," continued Blair. "Its patient-friendly features and the ability for patients to easily self-administer open new opportunities to move treatments out of the clinic and into the patient's own home. We are looking forward to working with pharmaceutical partners to provide this microneedle drug delivery alternative."

Disclaimer: Initiation of clinical studies may require a submission for regulatory review. For more information, visit 3M.com/dds or contact 1-800-643-8086.

Moberg Pharma's Fungal Nail Product Approved in China

Business Wire: January 27, 2015 – STOCKHOLM, Sweden – Moberg Pharma AB (OMX: MOB) today announced that its partner, Menarini Asia-Pacific, has received approval for Moberg's fungal nail product in China. Launch preparations in several markets are progressing ahead of plan.

Moberg Pharma's distribution agreement with the Menarini Group—a top 40 global pharmaceutical company—includes Italy, China, and eight countries in Southeast Asia. Menarini has in addition initiated launch activities in Malaysia, Singapore, and Hong Kong, and preparations are ongoing in the other markets in the region.

"We are excited about the progress that Menarini Asia-Pacific has made in registration and launch preparation activities. Kerasal Nail® has significant potential in the region. Assuming successful launches, the region will be an important contributor to revenues and earnings from 2015 and onward," said Peter Wolpert, CEO of Moberg Pharma AB. ■

Controlled Release Society
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Calendar of Events

2015

2015 CC-CRS/CSPS Joint Conference
Sponsored by CRS
May 26–28
Toronto, Canada
http://cc-crs.com/CRS

1st International Congress of the Controlled Release Society – Greek Local Chapter
Sponsored by CRS
May 27–28
Athens, Greece
www.afea.gr/event.asp?pid=146&lng=1

Controlled Release Technology: Delivery Systems for Pharmaceuticals, Proteins, and Other Agents
June 8–12
Cambridge, MA, U.S.A.
http://web.mit.edu/professional/short-programs/courses/controlled_release_technology.html

42nd Annual Meeting & Exposition of the Controlled Release Society
July 26–29
Edinburgh, Scotland, U.K.
controlledreleasesociety.org

Advances in Tissue Engineering Short Course
Sponsored by CRS
August 12–15
Houston, TX, U.S.A.
http://tissue.rice.edu/

Formulation, Processing, and Testing of Functionally Coated Multiparticulates Workshop
Sponsored by CRS
October 24
Orlando, FL, U.S.A.
controlledreleasesociety.org