CRS Leading Delivery Science and Technology

Newsletter

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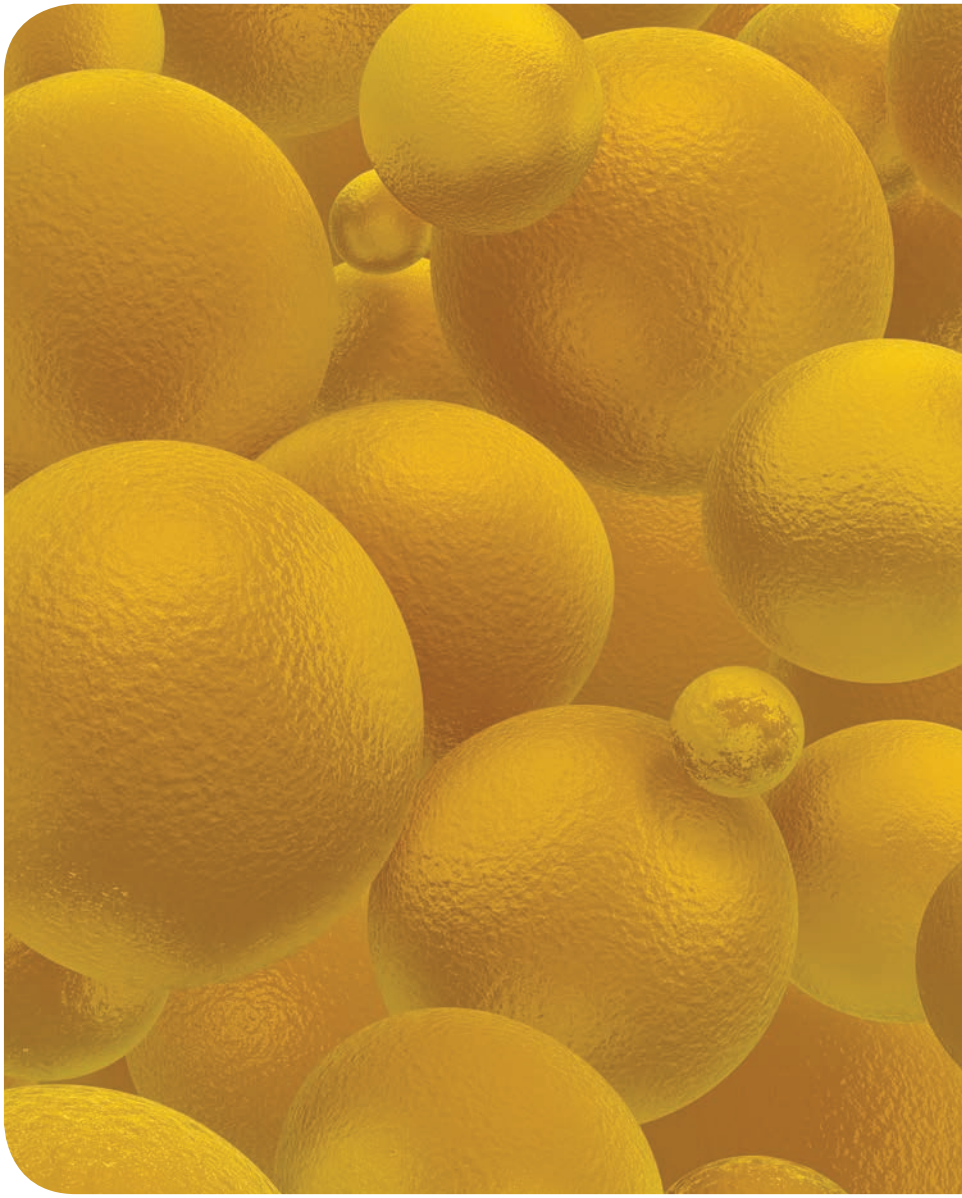
What's Inside



CRS Annual Meeting and Exposition

July 13–16, 2014 • Chicago, Illinois, U.S.A.

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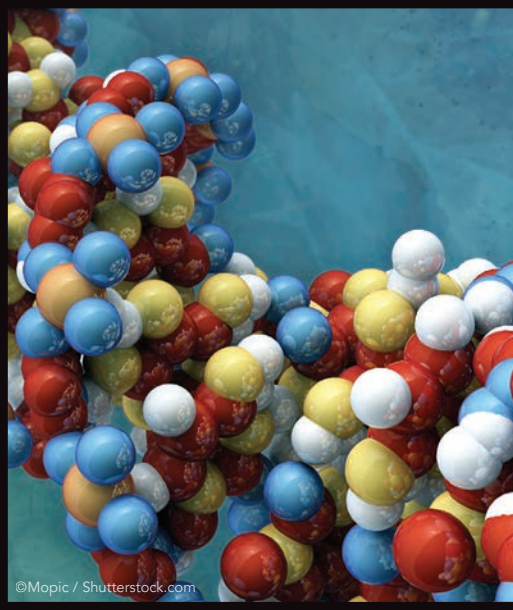
Access the Best in Delivery Science

Join us in Chicago to connect with those in the discovery, development, and delivery continuum.

- Learn from world-renowned researchers and thought leaders.
- Be a part of the global discussion on matters that affect the future of our science.
- Visit the exposition for the newest technologies, products, and services.
- Connect with colleagues from around the world.



Exposition Space and Sponsorships Available

TRANSLATION

of Delivery Technology:
Innovation to Commercialization

controlledreleasesociety.org

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CRS Newsletter

Leading Delivery Science and Technology

Vol. 31 • No. 2 • 2014

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

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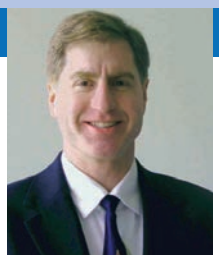
Visit controlledreleasesociety.org or e-mail crs@scisoc.org on questions about membership, meetings, publications, and services.

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



Steven Giannos
Independent Consultant
Baltimore, MD, U.S.A.

Crossing Boundaries/Crossing Barriers

One of the major hurdles for controlled release technologies is overcoming the biological barriers encountered in animals and plants. Stratum corneum and epithelium are only two of many boundaries and barriers where strategic methods must be developed to deliver drugs and nutrients effectively.

This issue of the *CRS Newsletter* contains interviews with two prominent scientists in our field of controlled release. Claus-Michael Lehr, the head of the Department of Biopharmaceutics and Pharmaceutical Technology at Saarland University in Germany and cofounder and head of the Helmholtz Institute of Pharmaceutical Research Saarland (HIPS), discusses his work with Across Barriers. Dr. Lehr is a prominent leader in the field of exploring biological barriers (especially the gastrointestinal tract, skin, and lungs) and finding appropriate carriers capable of transporting molecules efficiently across these barriers.

In another interview, Nancy A. Monteiro-Riviere, one of the world's leading nanotoxicologists in the field of investigative dermatology with an extensive understanding on the topic of engineered nanomaterials' effects on human health and the environment, discusses her career and recent move to Kansas State University.

In Scientifically Speaking, Randall Mrsny and David Brayden announce the workshop on Oral Delivery of Peptides and Proteins that will be presented at the 2014 CRS Annual Meeting in Chicago. The symposium will provide a forum to present recent information related to solving the challenge of efficient oral peptide delivery.

In another article, Papen-Botterhuis *et al.* share their findings on a new type of encapsulation material composed of a combination of a hydrophobic matrix material combined with crystalline nanoparticles to create oxygen protection under humid conditions. All selected components are generally recognized as safe (GRAS) for use in food products and can be dissolved or digested under gastrointestinal conditions to allow release of the encapsulated ingredient.

Additionally, Ouyang *et al.* discuss their work in computational pharmaceutics and the application of computer modeling to drug delivery.

The Preclinical Sciences & Animal Health (PSAH) Division of CRS announces a new expert panel initiative within their division. The PSAH Division is a multidisciplinary, international group of CRS members dedicated to advancing the science and technology of controlled release relating to preclinical sciences and animal health. The division aims to foster opportunities for collaboration between CRS members interested in animal and human health.

Also, we have a report from the CRS New Zealand Local Chapter (NZCRS). They organized a one-day symposium as part of the 2013 annual Australasian Pharmaceutical Science Association (APSA) conference, which was held on December 8–11. The symposium included invited and contributed speakers from as far afield as the United States, Denmark, China, and of course New Zealand.

I hope you are getting ready for Chicago.

Cheers,
Steven ■

Ian Tucker
University of Otago
Dunedin, New Zealand

CRS Grows Its Leaders

Every time I read the contents page of the *CRS Newsletter*, I think to myself, this society is going places—good places, that is—thanks to the efforts of many individuals and the relevance and importance of our science and technology. Data about the growing size of the CR market may excite us, but in my view personal stories about how a CR technology has improved the life of a close friend, relative, or yourself is what brings emotional enthusiasm and commitment to our science and technology. I think we should share these stories more than we do, and perhaps CRS could be a conduit for this.

Committee Reports Chart the Future
In March, the various CRS committees and task forces are submitting their reports, which address the charges (challenges) given to them by the Board in the second half of 2013. I am looking forward to each and every report, since each clearly meshes with the Strategic Plan for 2012–2017, and I await with particular enthusiasm and expectation the report from the Board of Scientific Advisors (BSA). You may recall that the BSA was charged with doing some horizon-scanning on where CRS science is likely to go in the next 5–10 years and with exploring developments in the fundamental sciences that may underpin and enable our delivery science in the distant future (>10 years). Given the concentration of knowledge and experience on our BSA, this will be an instructive report. Highlights from it will appear in a future *CRS Newsletter*.

Making Volunteering Valuable
We have committees, task forces, and boards (the Board and BSA), but in a busy world with ever-increasing demands on effective people, we need to continually analyse the way we do things and ask ourselves, "is there a better way?" Many organisations are replacing some of their committees with task forces that are given tightly defined, time-limited tasks, an approach that has some appeal to busy people. I suspect the approach we should use will vary with the task or charge at hand. For some challenges it will be a committee, for others a task force, or perhaps even an individual member or champion, while for others it will be done by our highly skilled staff. Such was the case recently when our headquarters staff developed an e-learning business plan for us. However, one committee that we will not replace is the Finance Committee.

Finance Committee: More Than Just Finances
The Finance Committee has both strategic charges and recurring responsibilities, which means it is active throughout the year. Its recurring activities include preparing a draft budget aligned with the strategic plan, monitoring our performance against the budget, keeping an eye on expenditure, overseeing our legal/tax responsibilities, liaising with the auditor, monitoring our investment strategy and our contracts, updating our risk management plan, and reporting to the Board at least quarterly. In addition to these recurring activities, this hard-working committee has also responded to requests from the Board to develop both a business plan for non-U.S./non-EU conferences and a robust process for selecting the sites of annual conferences. Although the Finance Committee develops these plans, the plans encompass far more than just financial issues. Other criteria include accessibility of the venue, appeal to members and exhibitors, hotels, facilities for the meeting and exhibitors, presence of an active local chapter, and so on. Based on the work of the Finance Committee, I believe the Board is able to make sound decisions that are in the best interests of the society and the membership.

It is a pleasure to acknowledge the detailed and astute work that has been done by the Finance Committee over the last two years under the able leadership of Tom Redelmeier (immediate past Treasurer) and Marcus Brewster (Treasurer), and we look forward to this work continuing under Ruth Schmid (Treasurer-Elect).

Elections
The Board has serious responsibilities for governance of CRS (strategic, legal, financial, evaluating management, succession planning, and so on) aimed at ensuring an effective CRS to serve the membership now and in the future. The importance of succession planning cannot be overestimated. The Volunteer Recruitment Committee is developing processes that will give members opportunity to actively contribute through effective volunteering and, importantly, to provide a pathway for development of leadership skills, team orientation, ability to understand constructive conflict, and a capacity for forward thinking. This will ensure we can continue to have a slate of strong candidates for the elected positions.

I encourage all members to actively participate in this year's election. The leadership of CRS is in your hands.

Ian Tucker
President ■

Discover the Latest at the 41st CRS Annual Meeting & Exposition

July 13–16, 2014 • Chicago, Illinois, U.S.A.

With a stellar scientific line-up, including more than 120 oral presentations, over 600 posters, five scientific workshops, and three insightful plenary speakers, the CRS annual meeting is the must-attend event of the year! Discover the latest findings in your area of delivery science, and expand your knowledge of other areas so that you can apply their technologies to your own work. Read here about the offerings in Consumer & Diversified Products (C&DP), Preclinical Sciences & Animal Health (PSAH), workshops that will add to your educational experience, and business opportunities at CRS Innovation Sunday.

C&DP Chair Nicole Papen-Botterhuis leads the 2013 C&DP luncheon.

C&DP Sessions Deliver a Wide Range of Applications

The C&DP Division focuses on encapsulation and controlled release research for food, nutraceuticals, personal care, cosmetics, home care, agriculture, textiles, and coatings. They have helped create programming specifically designed to meet the division's needs. This year's C&DP program is exceptionally strong, emphasizing the many areas that delivery science influences:

- "Advances in Process Engineering—New Methods for the Production of Particles, Capsules, and Coatings," featuring invited speaker Abhijit Gokhale (Patheon, U.S.A.), provides the information you need on improvements in established technologies.
- "Controlled Release of Actives in Consumer Products," with invited speaker Nilesh Shah (Dow Chemical, U.S.A.), covers recent developments in controlled release strategies in a diverse range of personal and home care areas.
- "Controlled Release Applications in Food, Feed, and Beverages," featuring invited speaker Erich Windhab (ETH Zürich, Switzerland), covers recent developments that benefit consumers and also helps companies leverage the new technology.
- "Evaluation and Characterization of Controlled Release Products and Production Processes," with invited speaker Lew Brown (Fluid Imaging Technologies, U.S.A.), focuses on identifying reproducible and relevant characterization of products and controlling production through appropriate electronic and analytical technologies.

At the mini-symposium "Micro- and Nano-Encapsulation: From Innovation to Commercialization," gain insight into today's industrial chemical and physical encapsulation technologies with emphasis on practical and physical limits, scale-up challenges, and costs.

Network with your colleagues at the C&DP Division Luncheon on Tuesday, July 15, at the Hilton Chicago.

PSAH Sessions Highlight Differences Between Species

The PSAH Division meets the needs not only of scientists involved in the development and regulation of drugs and biologics for veterinary use but also the interests of pharmaceutical scientists working in preclinical drug development. Opportunities abound to discover top science in both related areas at this year's CRS Annual Meeting.

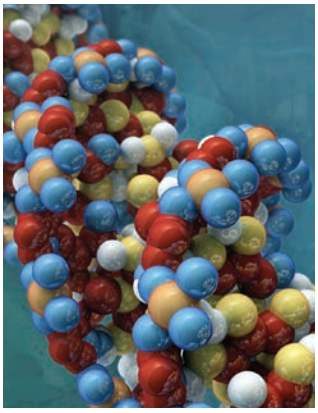
Examine why dosing concepts in different species have to be carefully evaluated with few assumptions, except that they are unlikely to correlate well, at the mini-symposium on "Interspecies Clinical Pharmacology Dosing Concepts."

Invited speaker Susan Cady (Merial Ltd., U.S.A.) headlines the session on "Novel Developments in Formulation, Analytical Chemistry, and Processing in Animal Health and Preclinical Sciences," which highlights current global research, development, and commercialization of controlled release technology in the preclinical and animal health sciences. Likewise, invited speaker James Birchall (University of Cardiff, United Kingdom) will lead off the session on "Predictive Animal Models for Assessing Long-Acting Formulations for Human and Animal Health and Their Challenges," which focuses on utilizing animal models for correlating between species and the complications that arise in their use.

All meeting attendees interested in preclinical sciences and animal health are welcome at the annual PSAH Networking Get-Together on Monday, July 14, at Chicago's premier blues club, Buddy Guy's Legends. Finish off a day full of science by meeting colleagues with the same interests in a relaxed setting.

>>> Visit controlledreleasesociety.org for information on the 14 scientific sessions and three mini-symposia focusing on bioactives.

Enhance Your Meeting Experience with a Workshop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Come early and attend one of the workshops at the 41st CRS Annual Meeting & Exposition. These workshops offer focused presentations on specific topics by noted speakers and are open to a limited number of participants for an additional fee. The workshops will be held Saturday, July 12–Sunday, July 13. You must register for workshops in advance, and you do not need to attend the entire meeting to attend a workshop. See the meeting website for more complete details, including schedules and lists of invited speakers.

Albumin: The Next Generation Protein Therapeutic

Saturday, July 12, 08:45 – 17:00

Organizers: Kenneth Howard, Aarhus University, Denmark, and Daniel Shelly, Novozymes Biopharma US, Inc., U.S.A.

Albumin is the most abundant human plasma protein that exhibits prolonged circulatory half-life and a predominant role in extracellular and intracellular transport of nutrients. Exploitation of these properties can be utilized for delivery of drug cargos and is a paradigm shift in control of drug extended half-life and targeted delivery. This workshop assembles global leaders from both academia and industry in a unique forum to present and discuss the application of albumin in drug delivery. Biological mechanisms relevant for albumin drug delivery capabilities such as molecule binding, cellular receptor engagement and recycling, and its tuning through recombinant technology for modulation of pharmacokinetics are addressed. Clinical development and commercial albumin-based drug products such as albumin-binding prodrugs, genetic fusions, and nanoparticles highlight its emergence as the next-generation protein therapeutic.

Oral Delivery of Peptides and Proteins

Saturday, July 12, 08:00 – 17:00, and Sunday, July 13, 08:00 – 12:00

Organizers: David Brayden, University College Dublin, Ireland, and Randall Mrsny, University of Bath, United Kingdom

Oral delivery of peptides and proteins is regarded as one of the great challenges for drug delivery. After a slump in interest in the mid-1990s, at least 12 technologies with selected peptides are now in clinical trials. The workshop will assess the current status of this revitalized field, exploring how selected technologies work and whether they can be applied to a range of peptide and protein-based payloads. Key aspects to be discussed are the rationale for payload and technology selection, repeat oral dose toxicology, and arguments for parenteral-to-oral switching.

Nanotechnology – Process and Formulation, Characterization and Applications

Saturday, July 12, 08:00 – 17:00, and Sunday, July 13, 08:00 – 12:00

Organizers: Teresa Virgallito, Microtek Laboratories, Inc., U.S.A., and Nicole Papen-Botterhuis, TNO, The Netherlands

Nanotechnology is a broad term that covers many areas of science, research, and technology. In the next 20 years, nanotechnology will touch the life of nearly every person on the planet. The workshop will provide an overview of nanoencapsulation and a range of applications where nanotechnology is being utilized. Future applications of nanotechnology will be discussed. The workshop will also cover regulatory compliance for nanotechnology for consumer products. Nanotechnology can be found in cosmetics, sunscreens, clothing, and many other consumer products today.

Computational Pharmaceutics – The Application of Computer Modeling in Drug Delivery

Sunday, July 13, 08:00 – 12:00

Organizers: Defang Ouyang, Aston University, United Kingdom, and Alex Bunker, University of Helsinki, Finland

This workshop will focus on the application of molecular modeling techniques in drug delivery—named as "computational pharmaceutics." The workshop will discuss the modeling of different drug delivery systems, such as cyclodextrins, solid dispersions, liposomes, polymer coating of delivery systems, particulate media, protein/peptide formulations, nonviral gene delivery systems and surface modification, and three important methodological areas: pharmacokinetic modeling, molecular modeling, and synchrotron radiation micro-computed tomography (SR-μCT) combined with the *in silico* 3D reconstruction.

Locally Acting Dermal Drug Products – Global Challenges for Development and Registration

Sunday, July 13, 08:00 – 12:00

Organizers: Howard Maibach, University of California, San Francisco, U.S.A., and Tapash Ghosh, ONDQA/CDER/FDA, U.S.A.

The workshop will bring a sound understanding of topical dermal products across multiple disciplines and multiple sectors with the goal of meeting the challenges of the 21st century. It will also discuss the challenges associated with demonstration of bioequivalence for topical products, from both new and generic drug perspectives, in light of the considerations for future regulatory submissions. Alternative and novel technologies for determining bioequivalence of topical drug products, as well as the value of *in vitro* drug release in semisolid dosage forms, will also be discussed.

CRS Innovation Sunday: Delivery Science Meets Business Opportunities!

CRS Innovation Sunday is all about the business of delivery science, taking innovative ideas and technologies into the commercial sector. All of the sessions give you important new information on companies and technologies as well as great opportunities for networking face-to-face. This is the start of the CRS Annual Meeting program—don't miss it!

Presenters from around the world highlighted new ideas, opportunities, products, and trends during the 2013 CRS Innovation Sunday.

Technology Forums

Are you interested in learning more about a company's research and products? Interested in a new technology from the company that developed it? Open to all registered attendees, Technology Forums give you the opportunity to gain in-depth information presented by the hosting company. Presentation titles, details, and speakers are posted on the CRS Innovation Sunday webpage for these participating companies:

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Soapbox Sessions

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What's new in delivery science? Come to the program where presenters "get up on their soapbox" to give you a quick glimpse of some of the most innovative technologies and products in development today. Linger to network with the presenters as you enjoy refreshments, with thanks to our sponsor. Soapbox applications will be received and reviewed until the session is full. Watch the CRS Innovation Sunday webpage for topics and presenters.

Industry Roundtable: Patient Adherence and the Future of Innovative Drug Delivery

Patient non-adherence to medication takes a huge toll on healthcare budgets and on human health. Estimates indicate that in the United States alone, non-adherence to prescription regimens wastes roughly $300 billion in healthcare system costs and results in approximately 125,000 preventable deaths each year. Solving the adherence challenge is now as critical as finding the next new drug and will profoundly impact the future direction of drug delivery. This Industry Roundtable will discuss perspectives and provide insight on the latest innovative delivery technologies, devices, packaging, patient interactive feedback systems, and other future strategies to increase patient adherence and improve treatment outcomes.

Exposition Grand Opening & Welcome Reception

CRS Innovation Sunday culminates in the Exposition Hall, where discovery, solutions, opportunities, and refreshments await you! Sunday evening features the Exposition Grand Opening & Welcome Reception. The Exposition/Poster Hall will also be open Monday and Tuesday as the central hub for poster viewing, program breaks, and refreshments. Be sure to thank the CRS Café Sponsors (*) for providing complimentary beverages.

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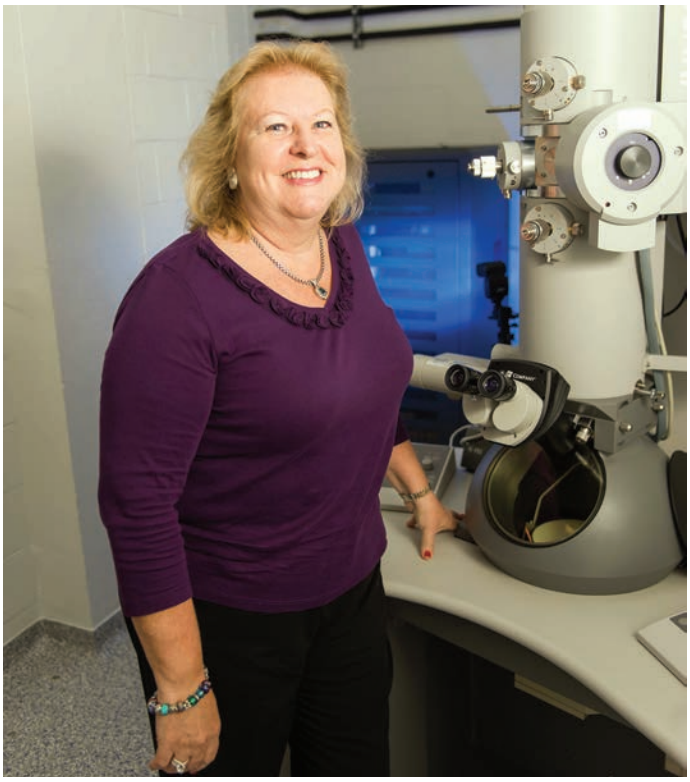
An Interview with Dr. Nancy Monteiro-Riviere, Director of the Nanotechnology Innovation Center at Kansas State University[1]

Vishwas Rai[2] and Bozena B. Michniak-Kohn[3]

Dr. Nancy A. Monteiro-Riviere is a Regents Distinguished Research Scholar and University Distinguished Professor of Toxicology and is one of the world's leading nanotoxicologists in the field of investigative dermatology with an extensive understanding on the topic of engineered nanomaterials' effects on human health and the environment. She is a pioneer in the field of safety assessment of nanomaterials. She has assessed the interactions and toxicity of environmental chemicals, drugs, and engineered nanomaterials using novel *in vivo* and *in vitro* methods, focusing on their skin absorption, penetration, and toxicity. In addition to this nanotechnology-focused research, she currently is developing alternative *in silico* and *in vitro* methods to study the safety of new dietary ingredients in pet food for dogs.

She has received more than $14 million in research funding from the National Institutes of Environmental Health Sciences, agencies of the Department of Defense, the Environmental Protection Agency (EPA), and other federal and industrial sponsors. She has presented her research at 145 international and national meetings and published over 280 manuscripts and book chapters in the fields of skin toxicology and nanotoxicology. Her work has been cited over 5,500 times. She is an editor of the books *Toxicology of the Skin* (Target Organ Series), *Nanotoxicology: Characterization, Dosing and Health Effects*, and the second edition of *Nanotoxicology: Progress Toward Nanomedicine*. She has trained numerous graduate students and postdoctoral fellows. In addition to being an associate editor for the journals *WIREs Nanomedicine & Nanobiotechnology* and *Materials Science and Engineering: C*, she serves on six editorial boards. She has also served on several national and international panels, including many in nanotoxicology for the National Research Council of the National Academies, the International Council on Nanotechnology, and NATO Advanced Research Workshop on Nanomaterials.



Monteiro-Riviere with her new TEM scope.

Dr. Monteiro-Riviere is a fellow in the American College of Toxicology and the Academy of Toxicological Sciences, where she was elected to its board of directors. She is a past president of both the dermal toxicology and *in vitro* toxicology specialty sections of the National Society of Toxicology.

She received Ph.D. in anatomy and cell biology from Purdue University, U.S.A., in 1981, followed by a two-year postdoctoral fellowship in toxicology at the Chemical Industry Institute of Toxicology (CIIT). She served North Carolina State University (NCSU) for over 28 years, culminating as a professor of investigative dermatology and toxicology. She is also an Emeritus professor at NCSU and a professor in the UNC/NCSU Joint Department of Biomedical Engineering and a research adjunct professor of dermatology at UNC School of Medicine. She established the new Nanotechnology Innovation Center of Kansas State University (KSU) in 2012, where she currently is in the process of hiring new faculty members.

Q *Please tell us about your undergraduate degree in science with a biology major. How did that shape your future career?*

A I had a great undergraduate education in the basic sciences and fell in love with comparative anatomy at Stonehill College in North Easton, Massachusetts, which is a small private Catholic college founded by the Holy Cross fathers. My experience stimulated me to enter graduate school and to pursue a degree in that field.

Q *How did you select Purdue University for higher studies? Tell us about your graduate research. Did you have any surprises, or was the experience as you had expected?*

1 Dr. Monteiro-Riviere can be contacted at +1.785.532.4367 or nmonteiro@ksu.edu.
2 Chrono Therapeutics Inc., Waltham, MA, U.S.A.
3 Ernest Mario School of Pharmacy, Rutgers–The State University of New Jersey, U.S.A.

A My husband and I had applied to several institutions. My husband wanted a DVM and a Ph.D. combined degree so he could understand the whole animal for research. We both had been accepted at the University of Pennsylvania and Cornell University, but then Purdue offered us full scholarships. We were newly married and did not want to go into debt. Purdue made it a lot easier to make that decision! It had a veterinary college, and Indiana University Medical School was also located in that department. I had the best of both worlds, because I took all the veterinary gross and microscopic anatomy and neuroanatomy courses, but I also had all the human gross anatomy, human neuroanatomy, and human histology exposure. I wanted to be the best comparative anatomist.

Q *What was the topic of your doctoral research?*

A I studied the ultrastructural development of nerve fibers in the skin of pigs. During this time I helped to discover a new smooth muscle in porcine skin, which we termed "musculus interfollicularis" or interfollicular smooth muscle based upon its location and attachments. This muscle is found midway between the level of the sebaceous gland and the apocrine sweat gland, and it spans the triad of hair follicles. We postulated that this muscle upon contraction draws the base of the aligned follicles together into a triangular conformation and rotates the outer two follicles of the triad. It was exciting to discover a new muscle in an animal that has been extensively studied for decades.

Q *What was the topic of your postdoctoral research? What made you choose your postdoctoral research topic(s)?*

A My postdoctoral fellowship was at CIIT in Research Triangle Park, North Carolina. CIIT conducted many inhalation studies on numerous chemicals. I studied the pathogenesis of chemically induced toxicity of the respiratory system with special reference to the nasal passages. Since my degree was in comparative veterinary anatomy and cell biology, I felt well versed in all aspects of anatomy. I studied the ultrastructural characterization of the nasal respiratory epithelium in the rat. I conducted macroscopic, microscopic, and ultrastructural anatomy studies on the rat nasal cavity, which revealed three new cell types: nonciliated columnar, cuboidal, and brush cells that were not previously characterized in the rat nasal mucosa. Then I evaluated the acute toxicity of the rat respiratory epithelium exposed to formaldehyde gas.

Q *From a modern-day perspective in which most scientists stay for only a few years in any one position, you spent 28 years at NCSU. That is quite an achievement.*

A It all depends on how you look at it. I never thought I would stay at NCSU that long. It was located down south, and I was from Massachusetts and wanted to go back home with family. I still prefer the north, but once at NCSU, we adjusted to the hot and humid climate. We loved being close to the ocean and the beautiful Outer Banks of North Carolina. We enjoyed our new positions and made lifelong friends. Both my husband and I had several job opportunities in the past, and at times we did some hard thinking and were prepared to move. I felt as if the ocean kept calling us back. We built a beach home on the Outer Banks, which reminded us of home. However, we decided to stay in the area because we had started a family and were both comfortable in our jobs. We had some large grants, were publishing with great colleagues, and had a great team of technical staff.

Q *Looking back, do you regret staying at one institution for such a long time?*

A Staying at one institution has some positives and negatives. I think we could have moved ahead faster if we moved a few times, but we would also not have had the opportunity to develop mature research programs. There are obvious trade-offs in any decision we make.

Q *Please share any advice for the upcoming generation of professionals heading to academic positions.*

A Academia is the only environment I have experienced, so I don't have anything else to compare it with. I felt that I did great in academia, but I do have the entrepreneurial spirit. In the early 1990s, we were approached to start our own company and looked into that for a while, but we were apprehensive about leaving two tenure-track positions and a great technical team, and of course relocating three small children! My career decisions were always made in the context of family. Staying at NCSU for so long did allow roots to be established and thereby provided stability for our family.

Q *Please provide readers with a summary of your research work at NCSU. What were some of the highlights and their outcome? Any disappointments?*

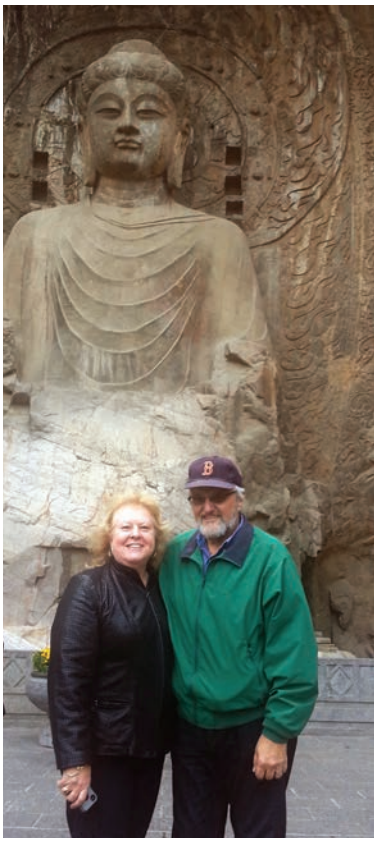
A My research at NCSU focused on skin drug delivery, toxicity, and nanotoxicology research. Initially, I was very interested in skin toxicology, whether it was assessing *in vivo* toxicity, skin absorption, dermal penetration, or *in vitro* toxicity of chemicals. I also was interested in working with 3D models of skin and assessed many of them for toxicity and absorption. I conducted numerous skin absorption and toxicity studies for industrial and pharmaceutical sponsors and the Department of Defense with chemical agents, pesticides, and jet fuels.

Over the years, my research area has shifted from chemical percutaneous absorption and toxicity to nanotoxicology. Nanomaterials are the building blocks of the next industrial revolution according to President Clinton's National Nanotechnology Initiative in 2000. Nanomaterials have attracted a great deal of attention because they are stronger than steel but at a fraction of the weight. Nanoparticles, when engineered appropriately, exhibit a variety of unique and tunable chemical and physical properties. These characteristics have made engineered nanoparticles central components in an array of emerging technologies. These unique properties may also result in similarly unique biological effects. Although they

Monteiro-Riviere interview continued on page 10

Monteiro-Riviere interview continued from page 9

have widespread potential applications in material sciences and engineering, the toxicology of these components has not been thoroughly evaluated under environmental and occupational exposure scenarios.



Nancy Monteiro-Riviere with her husband, Jim Riviere, visiting Longmen Grottoes in China.

A major issue is the health impact to humans exposed to nanomaterials by dermal routes. There is limited literature available on the toxicology of unmodified manufactured nanoparticles. Since there is limited information on how nanotubes can react with living cells, our laboratory has assessed the interaction between multi-walled carbon nanotubes (MWCNTs) and human epidermal keratinocytes (HEKs) using transmission electron microscopy and the release of the proinflammatory cytokine interleukin 8 (IL-8) as an early marker of biological response. We have reported that chemically unmodified MWCNTs were present within cytoplasmic vacuoles of the HEKs at all the time points. The MWCNTs also induced the release of the proinflammatory cytokine IL-8 from HEKs in a time-dependent manner. The data clearly showed that MWCNTs, not derivatized nor optimized for biological applications, were capable of both localizing within and initiating an irritation response in a target epithelial cell, a primary route of occupational exposure for manufactured nanotubes.

This research was nationally and internationally recognized, incorporated into a nanotechnology exhibit at the London Science Museum, and highlighted in *Science*. The manuscript, published in *Toxicology Letters*, was the journal's most cited paper for five years. This was an exciting feeling. A second well-cited paper in *Toxicology and Applied Pharmacology* detailed the interaction of nanoparticles with assay markers to cause erroneous results with classic cell viability assays. *Science Direct* identified this as one of their 10 Hottest Articles in 2010. I will continue to study dermal penetration and to assess cutaneous toxicology of many different types of nanomaterials. I hope to continue to have a leadership role in the field of consumer and occupational health exposure related to nanotechnology.
It was interesting how my nanomaterial research program began when I was an invited participant at the second annual National Academy of Sciences conference on "Designing Nanostructures at the Interface Between Biomedical and Physical Systems." This conference was to encourage interdisciplinary learning and to initiate research collaborations between active researchers in different disciplines. I was awarded a highly competitive grant from the Keck Futures Initiative with a Rice University collaborator, Dr. Andy Barron, which provided seed money to acquire preliminary data in nanotoxicology research. This was truly the seed that allowed my research program to grow.

Another seminal project that secured my international reputation in this emerging field was being a U.S. partner on the European Union NANOMMUNE Project based at the Karolinska Institute in Stockholm, Sweden. This has initiated friendships and collaborations that persist today.

Q *You have been doing a lot of traveling recently. Please share with us some highlights from your recent trips.*

A Of course, I attended the CRS Annual Meeting in Hawaii in July. My big trip was to Asia in October. I was invited to lecture at the National Center for Veterinary Drug Safety Evaluation and at the China Agricultural University in Beijing. I also traveled to speak at the 12th Chinese Society for Veterinary Pharmacology and Toxicology Congress in Zhengzhou. Then I lectured on the comparative anatomical factors that affect drug delivery at Huazhong Agricultural University in Wuhan. After that, I traveled further south to lecture at the South China Agricultural University in Guangzhou. Then I spent the weekend in Macau and moved on to Hong Kong and then Nagoya, Japan, to speak at the 6th International Symposium on Nanotechnology, Occupational and Environmental Health. Finally, I visited Tokyo for the first time. I saw many sites along the way and climbed the Great Wall of China, saw the Summer Palace, Forbidden City, Olympic sites, Beijing National Stadium, Temple of Heaven, and Tiananmen Square. I ate Peking duck, dumplings, and many different types of food. In Zhengzhou, I saw the Shaolin monastery; I saw the kung fu masters as well as the Pagoda Forest. In Wuhan, we climbed the Yellow Crane Tower and visited East Lake, the Hubei Museum, and the Botanical Gardens. Then we went to Luoyang to see the White Horse Temple and the large Buddhas at Longmen Grottoes. In Guangzhou, we took a cruise down the Pearl River and saw Canton Tower, Baiyun Mountain, and a Vegas-style show at the Chimelong International Circus. All of these places were fascinating, and we had wonderful hosts who took great care of us to make sure we had fun in between the lectures. I ate so many different things that they are too numerous to mention, but I did try snake. It really wasn't that bad, but do not eat the skin—that was terrible!

Q *Please list some of the most important publications from your lab that you feel have had the highest impact. Please let us know why you selected these particular journal articles.*

A Here are six journal articles selected for their impact and relevance in the field.

Monteiro-Riviere, NA, Nemanich, RJ, Inman, AO, Wang, YY, Riviere, JE. Multi-walled carbon nanotube interactions with human epidermal keratinocytes, Toxicol. Lett. 155: 377-384 (2005). This was one of the first papers that showed that nanomaterials not derivatized nor optimized for biological applications are capable of localizing within and initiating an irritation response in a target epithelial cell.

Monteiro-Riviere, NA, Inman, AO, Zhang, LW. Limitations and relative utility of screening assays to assess engineered nanoparticle toxicity in a human cell line, Toxicol. Appl. Pharmacol. 234: 222-235 (2009). This study showed that classic cytotoxicity assays can interact with nanoparticles to give inaccurate results, making extrapolating *in vitro* data to *in vivo* exposure or risk assessments problematic.

Ryman-Rasmussen, JP, Riviere, JE, Monteiro-Riviere, NA. Surface coatings determine cytotoxicity, and irritation potential of quantum dot nanoparticles in epidermal keratinocytes, J. Invest. Dermatol. 127: 143-153 (2007). This paper showed that the surface coating of nanoparticles is the primary determinant of cytotoxicity and immunotoxicity.

Zhang, LW, Monteiro-Riviere, NA. Mechanisms of quantum dot nanoparticle cellular uptake, Toxicol. Sci. 110: 138-155 (2009). This was one of the first papers that provided the mechanism of quantum dot nanoparticle cellular uptake and showed that the surface coating, size, and charge of these nanoparticles are important physicochemical parameters in determining cell uptake in mammalian cells for cancer diagnosis, cancer treatment, and drug delivery.

Monteiro-Riviere, NA, Wiench, K, Landsiedel, R, Schulte, S, Inman, AO, Riviere, JE. Safety evaluation of sunscreen formulations containing titanium dioxide and zinc oxide nanoparticles in UVB sunburned skin: An *in vitro* and *in vivo* study, Toxicol. Sci. 123: 264-280 (2011). Because of the concern that nanoparticles in sunscreens may be hazardous, this paper showed that *in vitro* and *in vivo* skin studies with titanium dioxide and zinc oxide formulations had minimal penetration but no transdermal absorption.

Xia, XR, Monteiro-Riviere, NA, Riviere, JE. An index for characterization of nanomaterials in biological systems, Nat. Nanotechnol. 5: 671-675 (2010). This study provided nanodescriptors for an adsorption index that can be used to develop pharmacokinetic and safety assessment models for nanomaterials.

Q *As a leader in the field of investigative dermatology, what are some of the primary challenges currently faced by the scientific community?*

A The need for human studies to assess the true safety of nanomaterials. *In vitro* and animal studies can only go so far.

Q *Please tell us about your recent move to KSU. What are some of your roles and responsibilities there?*

A I have only been at KSU for a little over one year. I was hired to establish a new nanotechnology research center from the ground up. This is an exciting opportunity. I spent the majority of my time trying to get my laboratory up and running. That means starting all over again by going out for bids for new equipment and ordering the new instruments and supplies. Setting up my new transmission and scanning electron microscopes took several months. This included working with engineers to create new rooms to house these scopes. Requesting permission from U.S. Customs and Border Protection and answering over 30 pages of questions on the uses of the TEM scope was quite a feat. During this time, I had to maintain my grant funding with EPA and an industrial sponsor and keep on task with reports. Moving to a new university meant that many tests were required for health and safety compliance, chemical safety compliance, and so on. I had to write more IACUC protocols and take over 40 modules of university procedures. We have a lot of new rules to follow. I had to hire a new lab manager, technicians, and postdoctoral fellows. This also meant writing new descriptions for these positions, preparing advertisements, selecting candidates, and making hiring decisions. In addition, I created my web page (nicks.ksu.edu). It meant a lot of busy work all at once rather than slowly over the years. Currently, I am in the process of selecting candidates for my EM scientist position and selecting seven new faculty members for our cluster hire for the new centers. However, this is an exciting and invigorating experience, because KSU has provided some 15,000 square feet of new space and substantial funding to initiate and sustain these new programs.

Q *Please share some of your views on personal and professional life management with young professionals.*

A My personal life management motto is to work hard but play hard too. I have raised three children (an engineer, a pharmacist, and a communication major) during my career. Now it is time for me to do what I want. So my husband and I started a new career by moving to Kansas with a new challenge of establishing new research centers.

Q *Do you have time for any particular hobbies?*

A What is that? I just about have time to read the newspaper. My husband and I love to go to Las Vegas occasionally. I enjoy going to our oceanfront beach home on the Outer Banks of North Carolina to walk on the beach, view the birds and dolphins, and sometimes we get lucky and see whales from our deck. I spend many hours on my deck reading and reviewing journal papers, grants, and so on. Thank God for the Internet: I can be reached anywhere and take conference calls from anywhere in the world while sitting on an oceanfront deck. ■

Crossing Barriers: An Interview with Claus-Michael Lehr

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

Claus-Michael Lehr is Professor of Biopharmaceutics and Pharmaceutical Technology at Saarland University in Germany and cofounder and department head of the Helmholtz Institute of Pharmaceutical Research Saarland (HIPS). Dr. Lehr is a prominent leader in the field of exploring biological barriers (especially the gastrointestinal tract, skin, and lungs) and finding appropriate carriers capable of transporting molecules efficiently across these barriers. Dr. Lehr was successful in the development of new *in vitro* models for these biological barriers based on epithelial cells and tissues. His laboratory developed the first *in vitro* model of the human alveolar epithelium. Dr. Lehr's research group also focuses on the site-specific action targeted delivery of specialized nano-sized drug carriers inside the body and on development of nanoparticle systems for *in vivo* tracking of molecules. He has published numerous findings in delivery of nanoparticulate drug carriers targeted to the inflamed colonic mucosa and cationic silica and chitosan-coated PLGA nanoparticles as a new technology platform for nonviral DNA delivery.

Prof. Lehr completed his Ph.D. in 1991 from Leiden University in the Netherlands and moved to Los Angeles for one year of postdoctoral research study. After working as a research associate in the Netherlands for one year, Dr. Lehr served as an associate professor at Phillips University in Marburg, Germany, for two years before becoming a full professor at Saarland University. Currently, Dr. Lehr maintains an active and well-funded research laboratory comprising scientists, assistant professors, multiple postdoctoral fellows, and undergraduate and graduate students. He receives his research funding from various European government and industrial agencies totaling over 1 million EUR per annum. Prof. Lehr has over 245 publications with multiple citations.

Claus-Michael Lehr and Julian Kirch receive the Phoenix Award.

The Lehr lab crew.

Dr. Lehr has many accomplishments and awards to his name. From CRS, he received the Graduate Student Research Award in 1991 and the Young Investigator Award in 2000. He was awarded the C. J. Kok Young Investigator Award at Leiden University in the Netherlands in 1993, the Phoenix Award in Pharmaceutical Technology in 2001, and the APV Research Award in the Pharmaceutical Sciences in 2006. Recently, he was honored with the International Prize of the Belgian Society of Pharmaceutical Sciences (2009), Research Award of Rhineland-Palatinate on Alternatives to Animal Testing, Dorothy Hagarthy Award for best paper in ATLA, fellowship in the American Association of Pharmaceutical Scientists (AAPS) (2010), and the German Federal Research Award on Alternatives to Animal Testing (2011). In 2013, Dr. Lehr became a fellow of the Controlled Release Society.

Q *Please tell us about your graduate school doctoral research.*

A This was a very exciting period scientifically, perhaps even my most productive one. After studying pharmacy in Germany, I had the chance to attend the newly founded Leiden-Amsterdam Centre for Drug Research (which opened after closing down the pharmacy program at Leiden University) as one of the first graduate students of the new centre. Cosupervised by two well-known professors in two different fields (Hans E. Junginger in pharmaceutical technology and Douwe D. Breimer in pharmacology), I was exactly at the interface between technology and biology that had always thrilled me most.

[1] Chrono Therapeutics Inc., Waltham, MA, U.S.A.
[2] Ernest Mario School of Pharmacy, Rutgers–The State University of New Jersey, U.S.A.

Q *How was your brief postdoctoral experience at the University of Southern California (USC)? Was there any specific reason for pursuing your career back in Europe?*

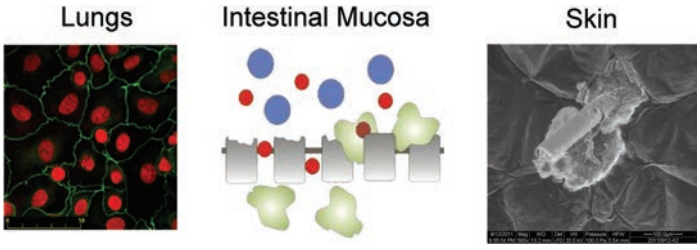
A After undergraduate and graduate studies in Europe, I wanted to experience the United States, both as a country and as a research environment. Los Angeles was an attractive place for a young family with two kids in preschool, and Prof. Vincent Lee was a fantastic mentor. The reason for pursuing my career back in Europe was mostly for personal reasons: with only some 10 vacation days per year, as was typical in the United States at that time, I foresaw enormous difficulties in regularly visiting my parents and other family back home.

Q *How would you compare pharmaceutical research (academic and industrial) in Germany with the United States?*

A Because I have limited personal experience from working in industry, I should probably better refrain from making comparisons at that level. Academically, however, the goals and tasks are rather similar, as they probably are everywhere in the world: academics strive for scientific excellence and wish to publish in high-ranking journals. At the same time, you must enjoy teaching students as well as trying to convince your peers of your ideas to get the necessary grant money. In addition, you must not be shy about accepting some administrative tasks and engaging in the scientific community and its various organizations at both the national and international level (for example, in CRS).

Q *As you know, government academic research funding has decreased to a great extent in the United States in the last couple of years. Have there been any drastic effects on academic funding in Germany and Europe, in general, in last couple of years?*

A Well, the funding situation probably brings us to differences between the United States and Europe, Germany in particular. Although research money has notoriously always been tight, it is not only in the United States that the competition for research money has become stiffer and stiffer. Luckily enough, investing in research and education is unanimously seen as most important for Germany by all relevant political parties. Also, the European Union significantly increased their research budget for the next five-year program. At the same time, however, the number of scientists competing for this money has also increased, because in other countries the economic development has not been so favorable.



Biological barriers such as lungs, intestinal mucosa, and skin have an important function to protect our bodies against toxins, microorganisms, and other environmental influences. These barriers must be overcome without taking damage so that drugs can reach their targets.

Q *Could you please guide younger academic faculty around Europe by elaborating on the primary research funding sources? Do these agencies also consider funding research outside Germany and Europe?*

A There are indeed some excellent possibilities, especially for younger scientists, to work in Europe, provided they are sufficiently mobile to move to other countries. The European Research Council has attractive programs for scientists in the beginning, middle, and advanced stages of their careers. You can propose as a research program essentially whatever you want, as long as you succeed in convincing peers that your plan is excellent. There are also top-down structured research programs sponsored by the European Union, in particular by the Innovative Medicines Initiative, a program cosponsored by the EU and the European Federation of Pharmaceutical Industries. They invest substantial amounts of research money that are most relevant to pharmaceutical sciences and also to drug delivery.

For undergraduate or graduate students as well as young postdocs, the German Academic Exchange Service (DAAD) and the Alexander von Humboldt Foundation (www.avh.de) have attractive programs to support the mobility of young scientists, both coming from and going to research labs abroad. DAAD sponsored my postdoctoral fellowship at USC.

Q *What are some of your future long- and short-term research directions with Helmholtz Centre for Infection Research?*

A Infectious diseases are an enormous problem worldwide, causing a quarter of all deaths, twice as many as cancer. Surprisingly, however, both the number of antibiotics approved and companies doing research on antibiotics have dwindled almost to zero during the past 20 years, while the number of bacterial and viral threats, and in particular bacterial resistance, is on a continuous rise. Delivering drugs to intracellular bacteria, coping with biofilms, or overcoming the cellular wall of gram negative bacteria are emerging but challenging tasks for drug delivery.

Q *How did Across Barriers GmbH and PharmBioTec GmbH begin? What are the goals of these companies?*

A I cofounded Across Barriers more than 10 years ago together with one of my first graduate students. At that time not only was it a favorable climate for such endeavors but also there were the right people who were looking for new professional alternatives compared with joining well-established big pharmaceutical companies. Although I am no longer actively involved, I am happy and proud that Across Barriers is still operational, now with some 30 employees. PharmBioTec

Lehr interview continued on page 14

Lehr interview continued from page 13

was not a private start but—interestingly enough—a 100% subsidiary of Saarland University. The three professors involved in the foundation of HIPS were also privileged to act as CEOs/CSOs for PharmBioTec, bringing in their know-how from different departments (biotechnology, medicinal chemistry, and drug delivery) along the typical drug development chain.

Q *Please tell us about the Galenos Network. Do you have any perspective on having a bigger (perhaps international) network like that? What might be the advantages and challenges?*

A The Galenos Network was a fantastic experience and an overwhelming success. What started as an informal collaboration of a handful of (at that time) young professors at several European universities suddenly became a success, with well-deserved recognition by the EU Marie Curie program with almost 2 million EUR funding. This allowed us to sponsor 40 Ph.D. candidates from all over the world to spend one year of their research in a partner lab of the Galenos Network, thus qualifying for the international distinction "Galenos Euro-Ph.D. in Advanced Drug Delivery." Apparently, we have been able to attract some of the most talented and ambitious graduate students, because about five years after finishing the program, almost one-third of its participants have meanwhile reached professorships or similar leading positions in the pharmaceutical industry.

Q *Could you give us some insight on the performance of the pharmaceutical industry in Germany (or Europe in general)? How has the Eurozone crisis affected the field? Please share your views.*

A As I said before, I see myself primarily as an academic scientist and shall be careful about sticking out my neck on industry-relevant questions. However, there is no doubt that Europe went through quite a significant financial crisis, although Germany somehow managed rather well even in such difficult years. Luckily, it seems that the worst is behind us. Compared with other industrial sectors, the pharmaceutical industry was probably not as affected by the crisis, but many companies used the opportunity to restructure their organization and portfolio, including some job cuts. But together with the hopefully upcoming end of the crisis, I expect that new job opportunities will come back again pretty soon.

Q *Please share a couple of the most influential articles coming out of your lab.*

A In the last year, I was most proud of our paper on the structure and barrier properties of mucus, which was accepted to *PNAS* and was a nice collaboration with some colleagues from our physics department. At the end of last year, it was selected for the Phoenix Award, which includes 10,000 EUR and is one of the most attractive awards in the pharmaceutical sciences in Germany. Another paper that I consider significant was the publication of a first clinical trial on targeting micro- and nanoparticles to inflamed mucosal areas in IBD patients, which appeared on the title page and in an editorial in the *Journal of Controlled Release*. In a recent paper in *Vaccine*, we showed that the follicular route might be a valid opportunity for systemic antigen delivery via the intact skin. This paper is also important to me because it shows our first success in moving into research areas that are relevant to infectious diseases.

Q *What are other research articles and areas that have influenced you in your career?*

A What I am fascinated by in drug delivery research is the intrinsic multidisciplinarity. Unfortunately, my time for reading is much more limited in my current position than I would have ever expected (or hoped) as a graduate student or postdoc. Still, however, I try to catch up with significant developments affecting the three biological barriers that my research focuses on: the gastrointestinal tract, skin, and lungs. I also am attracted by nanotechnology, although I would consider many novel nanomaterials as less than ideal candidates for new drugs or drug delivery systems. It remains an important task to investigate their safety and also potential risks for our environment and health. Here, we also try to make contributions outside the field of pharmaceutical sciences by offering our expertise on cell- and tissue-based *in vitro* models as collaboration partners in such research projects. As a collateral benefit, my team has also been able to contribute to research on alternatives to

Onboard the Temptation X.

animal testing. Our work was honored with the German Federal Research Award on Alternative Methods in 2010, and we just won last year's best paper award in *ALTEX*.

Q *Being an incredibly busy individual, please share your views about the balance of personal and professional life.*

A Keeping a reasonable work-life balance is most important to me. Although my kids have meanwhile grown up, I really enjoy the days when they are all at home or we can go together on some vacation. To stay physically fit and mentally stable, I also try to leave enough time for my two hobbies. As a sport I like sailing, either just for the weekends on a nearby lake in Saarland or on the ocean, where we successfully participated in a 24-hour race during Germany's famous Kiel Week. My other hobby is music. I enjoy going to concerts with my wife, but I also actively play drums, which I started as a child. With our jazz band the "Old Bony Dogs" we give a few concerts each year, mostly at smaller clubs or private parties, and a few weeks ago we just recorded our first CD.

Q *Can you tell us something about your family?*

A The most important person to me is probably my wife, especially since my mother passed away at the beginning of last year. Christine and I have been together since I was 15. She is a town-planning engineer, thus working in a totally different area than me. But this is sometimes quite helpful for both of us in our professional careers. Our children are Johanna (25), Saskia (23), and Felix (20). They are studying geophysics, medicine, and children's pedagogics, respectively, so neither of their parents could convince them to follow their respective professions. However, we enjoy and probably benefit from exchanging our thoughts and views on politics, daily life, and professional experiences that come from so many different perspectives. ■

Computational Pharmaceutics: The Application of Computer Modelling to Drug Delivery

Defang Ouyang,[1,2] Alex Bunker,[3] Amin Rostami,[4] and Jiwen Zhang[5]

Introduction

The use of computational modelling methods in the field of drug design—for example, quantitative structure–activity relationship (QSAR) and ligand docking—has over the past decade become well developed to the point of being a mature field.[1] Pharmaceutical research is, however, a far broader field than drug design alone; once a candidate drug molecule has been found, a method to deliver the molecule to the target site must be devised. Unlike the case for drug design, the application of computational modelling to drug delivery and pharmaceutical nanotechnology ("computational pharmaceutics") is a very new field with great potential for growth. Although a number of techniques have been developed for the analysis of dosage forms, the development of drug formulations still strongly relies on the personal experiences of scientists by trial and error.[2] Computational modelling has the ability to provide a multiscale window, potentially right down to the atomistic level of resolution, on our system, providing qualitative insight that in many cases is simply not available through experimental means alone.[3] As such, computational modelling techniques remain underutilized in the field of pharmaceutics, in comparison with, for example, drug design. The aim of this paper is to introduce a general audience of pharmaceutical scientists in both industry and academia to the application of computational modelling techniques on problems relating to pharmaceutics (drug delivery and nanomedicine). The paper will cover both the computational modelling methodologies used and several examples in which these methods have been applied successfully in this field, including molecular dynamics (MD) simulation, molecular modelling of PEGylated liposome-based delivery systems and of synchrotron radiation micro-computed tomography (SR-μCT), and structure reconstruction of drug delivery systems (DDSs).

Application of MD Simulation Techniques in Formulation Development

MD simulation techniques are able to help us to investigate the molecular mechanisms of drug delivery and then develop novel DDSs. For example, systematic investigations of the complexation process of siRNA-cationic polymer were performed by MD simulations, and their effects in gene release within the cytosol were analysed.[4–8] These novel simulations provide a much better understanding of key mechanistic aspects of gene-polycation complexation and thereby advance progress toward rational design of nonviral gene delivery systems, as shown in Figure 1. Another example is solid dispersion. MD simulation can help us to explore the physical state between polymer and drug in solid dispersion formulations, which strongly relate to the physical stability of solid dispersion.[9] As these examples show, MD simulation is a powerful technique for investigating the mechanism of drug delivery on the molecular level.

Molecular Modelling of PEGylated Liposome-Based Delivery Systems

So far the only clinically approved example of nanomedicine is Doxil,[10] the drug doxorubicin encapsulated in a PEGylated liposome. This consists of a lipid membrane in which some of the lipid headgroups have been functionalized with poly(ethylene glycol), PEGylation, to form a PEG corona around the liposome, which protects the liposome from the defence mechanisms of the human body. How PEG plays its role in inhibiting uptake by the immune system, and the interaction of PEG with targeting ligands on the surface of the liposome, is not completely understood and in many cases is impossible to investigate experimentally. Computational molecular modelling has been used to provide a window on this. Issues we have successfully addressed include the optimum

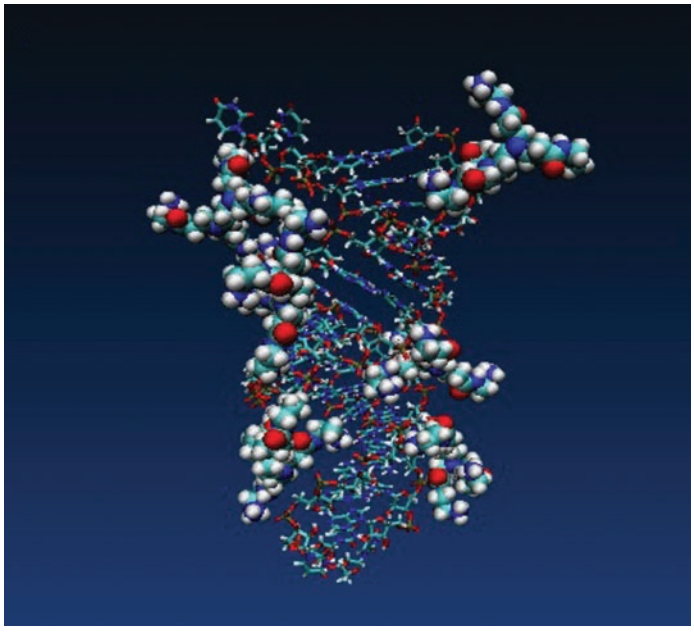


Figure 1. *Snapshots of 4+ polymer–siRNA complex at 10 ns at a charge ratio of 0.6/1 (molecular ratio 6/1).*

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[4] Manchester Pharmacy School, University of Manchester, United Kingdom.
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molar fraction of PEGylated lipids in the formulation, possible mechanisms of protection,[11] and a determination of why a new targeting moiety, successful in initial screening, fails when attached to a PEGylated liposome,[12] as shown in Figure 2. We have also studied the effect of cholesterol in the liposome membrane. This represents a case study in which molecular modelling has been used to gain real insight that can directly be applied to clinical formulation.

3D Structural Architecture of DDSs by SR-μCT and Structure Reconstruction

DDSs aim for good compliance, fewer side effects, and better efficacy than the conventional dosage forms. The three-dimensional (3D) structural architecture of a solid DDS is the primary parameter controlling drug release kinetics, but conventional ways to observe the constituent particles and dosage forms using instruments such as electron microscopes cannot quantitatively integrate the 3D information of a DDS with its release kinetics.[13] Because dosage forms such as tablets are prepared and formed under high pressure, it is difficult to determine the internal architecture without damage to the dosage form by conventional methods. A noninvasive *in situ* method such as SR-μCT combined with *in silico* 3D reconstruction is hopefully opening up a new understanding of DDSs, as shown in Figure 3.[13–15] Our research has demonstrated that SR-μCT is powerful in unmasking the 3D structure of DDSs with a new

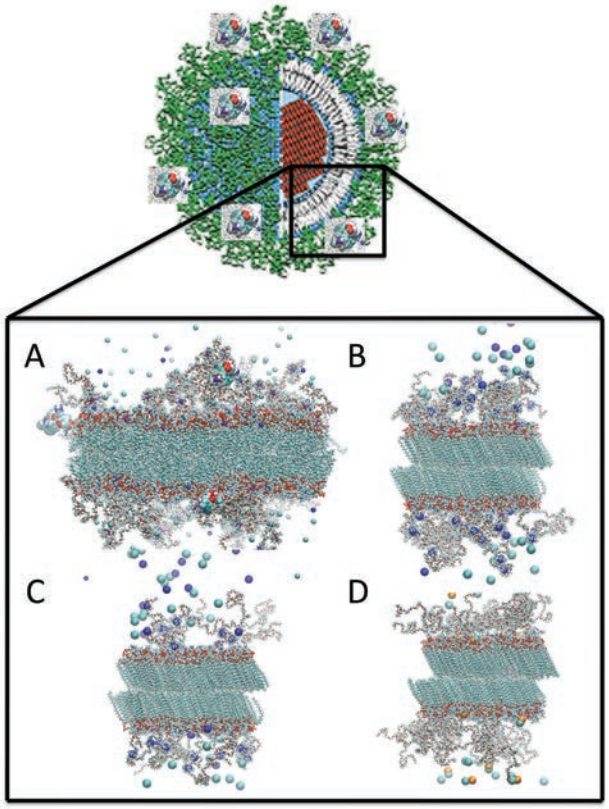

Figure 2. *Examples of simulations that have been performed studying the surface structure of the PEGylated liposome. Slabs of PEGylated membrane have been simulated as follows: with targeting ligand (A), in physiological NaCl concentration (B), varying the PEG density (C), and with calcium (D).*

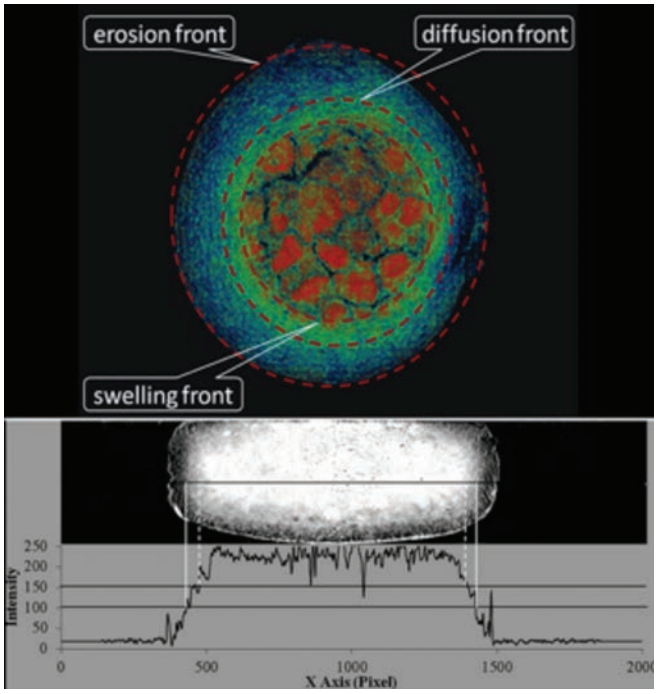

Figure 3. *A reconstructed quantitative 3D model of gel-forming matrix tablets.*

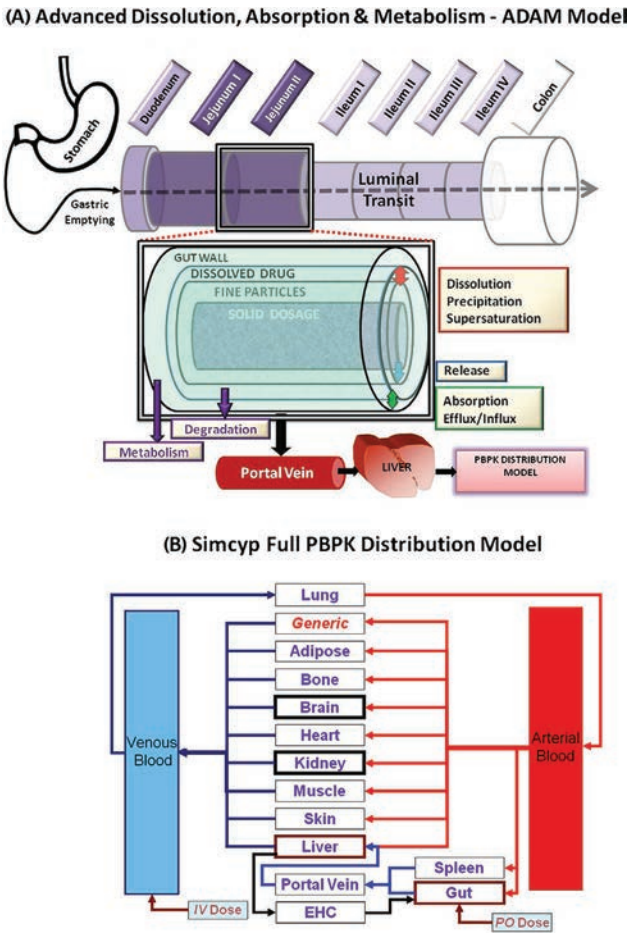

Figure 4. *Simcyp ADAM (A) and full physiologically based pharmacokinetic (B) distribution models.*

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vision. The extent of drug released can be correlated with the dynamic internal structure of the gel-forming matrix tablets, the monolithic osmotic pumps, and the sustained release pellets. The irregular internal structure of DDSs has been quantified by the fractal dimension and correlated well with drug release performance. Microstructures such as the shapes and locations of thousands of droplets and crystals within a tablet are simultaneously traced by the powerful methods. Therefore, the determination of 3D structural architecture by SR-μCT combined with *in silico* reconstruction unveils new characteristics of DDSs.

Population-Based Pharmacokinetic Modelling and Simulation

The population-based simulator streamlines drug development through the modelling and simulation of pharmacokinetics and pharmacodynamics in virtual populations. The simulator is used for the prediction of drug-drug interactions and pharmacokinetic outcomes in clinical populations, as shown in Figure 4.[16]

Conclusions

"Today the computer is just as important a tool for chemists as the test tube" (Nobel Prize in Chemistry 2013). As computer-aided drug design (rational drug design) has changed the paradigm of drug development in the past three decades, computational pharmaceutics will also be able to shift the paradigm of drug delivery research in the near future.

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Computational Pharmaceutics – The Application of Computer Modeling in Drug Delivery Workshop

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Organizers: Defang Ouyang, Aston University, United Kingdom, and Alex Bunker, University of Helsinki, Finland

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Oral Peptide Delivery

Randall Mrsny[1] and David Brayden[2]
Oral Peptide Workshop Cochairs, 2014 CRS Annual Meeting

There is no universally accepted definition for molecules that could be considered therapeutic peptides. Frequently, a therapeutic peptide is thought of as being composed of fewer than 50 amino acids that associate in solution to form bioactive materials without extensive tertiary structure. A number of these peptides have now been demonstrated to provide clinical benefit to patients for indications that include diabetes, osteoporosis, acromegaly, and ischaemic perfusion injury. The market for synthetic peptides alone has increased from $5 billion in 2003 to currently over $13 billion.[1] There are 100 peptides in clinical development, and over 400 are in preclinical research.[2] Currently, therapeutic peptides are most commonly delivered by subcutaneous (SC) injection. Although oral delivery is recognized as the preferred route for drug administration because of the extensive surface area of the gastrointestinal (GI) tract and its accessibility by oral formulation, this does not result in an acceptable outcome for most therapeutic peptides. Efforts have been made to reduce the rapid clearance of peptides from the body following injection as a way to reduce SC injection frequency by direct amino acid replacement, chemical coupling with lipids or polymers, or noncovalent association with polymers. These approaches will likely be acceptable for only a subset of these molecules owing to the nature of their biological actions.

There are several reasons to explain why administration by SC injection rather that oral delivery is currently the universal option for therapeutic peptides. First, most of these peptides are made from native L-amino acids that make them very sensitive to protease and peptidase activities of the stomach and small intestine that are present as part of normal digestion. Second, therapeutic peptides do not readily traverse the epithelia of the GI tract because of their physicochemical (large molecular weight and hydrophilic) properties. Many therapeutic peptides are potent agonists with a relatively narrow window separating a noneffective dose from one resulting in toxicity, so this means that the large intrasubject variability in pharmacokinetics seen with low oral bioavailability carries safety and efficacy risk. Finally, uptake of a drug following oral delivery typically occurs in the small intestine of the GI tract, which results in a direct vascular delivery to the liver due to uptake into the portal venous system. While some therapeutic peptides act in the liver, this organ is the primary site of systemic degradation of most other peptides. Thus, even if one can identify a platform approach to achieve oral peptide delivery, it will not result in an optimal outcome for all therapeutic peptides.

The desire and extensive efforts by the pharmaceutical industry to identify methods for the efficient and consistent oral administration of therapeutic peptides have been supported primarily by the rationale that people prefer to take oral medications relative to SC injection. Although convenience is an important factor, it is unlikely to be enough to justify a parenteral-to-oral switch, because most patients undergoing chronic injectable therapies are well used to ever-improving needle technology. There is the obvious perception that an oral product would dominate the marketplace. This is certainly the likely outcome, but *only* for a situation in which the oral product results in sufficiently consistent delivery to provide an acceptable safety-to-efficacy window and for the cost of the oral product to reasonably priced relative to the SC injection product. Thus, the requirements for a successful oral product demand consistency and relatively high efficiency of uptake into the body relative to SC injection. Numerous efforts have been made to replicate the functional properties of therapeutic peptides using stable small molecules or peptides prepared from nonnative materials that would improve GI tract stability and increase oral bioavailability. To date, small molecules have failed to replicate the complex receptor-binding properties required to mimic the physiological actions of therapeutic peptides, and nonnative peptides have not yet passed the rigorous tests of safety and efficacy required to qualify new chemical entities.

There are a variety of clinically approved technologies that can be used to stabilize therapeutic peptides through the gauntlet of harsh conditions in the stomach and the catabolic environment of the small intestine (Figure 1). Thus, there is currently a

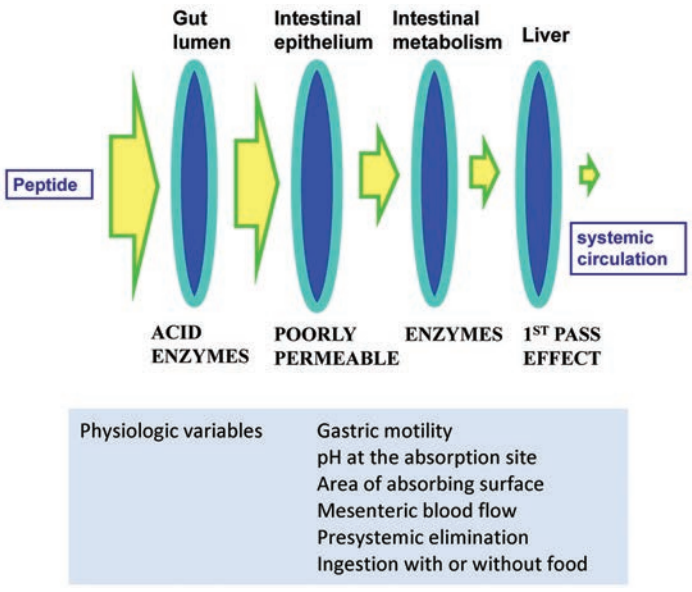

Figure 1. *The loss in oral bioavailability of peptides in the intestine resulting from metabolism, low epithelial permeability, and the liver first pass effect. The CRS Oral Peptide Workshop will address how each of these hurdles can be overcome by formulation approaches.*

Mrsny and Brayden Scientifically Speaking continued on page 20

[1]University of Bath, United Kingdom.
[2]University College Dublin, Ireland.

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significant focus on finding methods to overcome the barrier properties of the small intestinal epithelium. Previous efforts to achieve this have taken brute force approaches of adding agents that physically disrupt the epithelial barrier. One of these strategies, using a medium-chain fatty acid (capric acid) was even approved for a product given by rectal application to enhance the uptake of an antibiotic. Studies demonstrated that the extent of antibiotic uptake observed for this product correlated with the epithelial damage.[3] Clearly, there is a need to find more biologically compatible methods to facilitate the transport of therapeutic peptides in sufficient quantity across the intestinal epithelium that would be compatible with human physiology, especially if the patient is anticipated to take the drug daily or even multiple times a day. Therefore, the goal of many recent approaches involves manipulating endogenous elements of the small intestinal epithelium to produce subtle changes to the barrier that otherwise suppresses the uptake of molecules in the size range of therapeutic peptides.

The intestinal epithelium is organized as a single sheet of polarized cells that form a delicate yet formidable barrier to the casual uptake of molecules. This function is critical for maintaining water homeostasis (life-threatening secretory diarrhea results from extensive breaches of this function) and protection from the entry of unwanted materials (a number of materials in our diet would have biological actions if they were to be absorbed after ingestion). In the absence of causing overt damage to the epithelium, three general mechanisms of peptide transport across this barrier are possible: materials can move across bilayer membranes and through epithelial cells (transcytosis), through cells via vesicular transport (transcellular transport), or between adjacent epithelial cells (paracellular transport). As stated previously, efforts to emulate intestinal transcytosis achieved by small molecule drugs using similar sized compounds intended to replicate the biological activities of therapeutic peptides have been largely unsuccessful. Efforts to identify stable analogues of therapeutic peptides with the capability of efficient transcytosis have not yet delivered approved products.

Some approaches have examined vesicular trafficking to achieve transcellular transport, but this approach typically requires the chemical modification of the therapeutic peptide to allow its efficient entry into vesicles that shuttle from the luminal surface of epithelial cells to their basal surface, where release of the molecule will lead to uptake into the portal circulation. The same access to the body, achieved by enhancing the flux through the paracellular route, can be achieved without chemical modification to the therapeutic peptide. Paracellular transport is limited by a complex of proteins localized to the apical neck of polarized epithelial cells, a structure known as the tight junction (TJ). Initial efforts to modify TJ function have been achieved by empirical strategies with poorly defined mechanisms. Recent studies to deconstruct TJ structure/function relationships have been pursued. This strategy has provided the greatest interest with recent clinical information being obtained, some of which will be presented in case studies at the workshop at the CRS Annual Meeting in Chicago on July 12–13.

The goal of the workshop is to present recent information related to solving the challenge of efficient oral peptide delivery. Contributors will combine academics, major pharma, specialist oral drug delivery firms, consortia leaders, and regulatory experts. A short primer on oral peptide delivery appears in our recent commentary.[4]

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Oral Delivery of Peptides and Proteins Workshop

Saturday, July 12, 08:00 – 17:00, and
Sunday, July 13, 08:00 – 12:00
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- Lipid-Based Systems for Oral Peptides
- Pulsatile Delivery of an Oral PTH Analogue in Man
- Clinical Experience with an Oral Octreotide *"Transient Permeability Enhancer"* Formulation for Acromegaly
- TRANS-INT: A European Integrative Effort Towards Oral Peptide Delivery
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Nanotechnology for Encapsulation: Improved Barrier Materials for Protection of Oxygen-Sensitive Ingredients

N. E. Papen-Botterhuis, R. J. Van Ee, J. Eversdijk, J. W. Timmermans, T. M. Slaghek, and A. T. Ten Cate[1]

Introduction

Many ingredients in food and pharma products are sensitive to degradation by oxygen, leading to changes in taste or flavour, or even unhealthy effects. Microencapsulation of the ingredient, surrounding the ingredient with a shell material that prevents or reduces oxygen diffusion, can be used to create a longer shelf life for the envisioned product.[1,2] Different shell materials can be used, depending on the ingredient, the type of encapsulation technology, and the envisioned product. In particular, product and storage conditions with high humidity or water content pose challenges to the choice of shell material,[3] as this might swell or dissolve, thus strongly reducing the protective effect.

We have investigated a new type of encapsulation material that is composed of a combination of a hydrophobic matrix material combined with crystalline nanoparticles to create oxygen protection under humid conditions. All selected components are generally recognized as safe (GRAS) for use in food products and can be dissolved or digested in gastrointestinal conditions to allow release of the encapsulated ingredient (Figure 1).

Materials and Methods

A mixture of zein and lauric acid (70/30 w/w) was dissolved in an ethanol/water mixture (96/4 w/w) at 65°C. One solution was used as such, whereas calcium citrate nanoparticles (11w% or 21w% with respect to the zein/lauric acid) were dispersed in the other two. Subsequently, linseed oil was added and emulsions were obtained after sonification and used for spray-drying. As a reference, linseed oil was also encapsulated in gelatin matrix. This emulsion was prepared in the same way but at room temperature.

Microencapsulated linseed oil was produced by spray-drying with a Büchi B-290 mini spray dryer, under N_2 atmosphere.

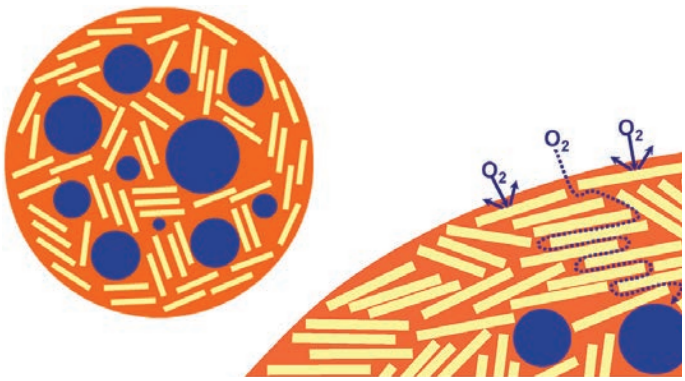

Figure 1. *Schematic of spray-dried particles containing an oxygen-sensitive oil, a biopolymer encapsulation matrix, and calcium citrate nanoparticles.*

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The obtained powder was stored at room temperature at 90% relative humidity, and stability of the encapsulated linseed oil was studied by monitoring the double bond conversion with FTIR spectroscopy. In a separate series of experiments, the powder (0.15 g) was mixed with carboxymethylcellulose (1.5 g), and water (25–29 g) or 1M NaCl solution (17–18 g) was added to create a hydrogel, stored at room temperature or 40°C, and stability of the linseed oil was again monitored by FTIR.

Results and Discussion

Zein, a hydrophobic plant protein, was selected as the major component for the shell material, because it combines good oxygen barrier properties with low swelling in the presence of water or water vapour.[4] It was mixed with lauric acid, which acts as a plasticizer to create a shell material with good film forming and mechanical properties. Crystalline calcium citrate nanoparticles were dispersed in the material to create an additional oxygen barrier as well as increased mechanical stability of the shell material under humid conditions.

Linseed oil was selected as the oxygen-sensitive model ingredient. It was encapsulated in the shell material by spray-drying, starting from an emulsion of the oil in ethanol/water mixture, in which the shell material was soluble at elevated temperature.

As a reference, linseed oil was also encapsulated in gelatin shell material. The obtained powders were stored in humid air (95% rh), and the presence of unsaturated bonds in the linseed oil was monitored by FTIR spectroscopy. It was found that no significant degradation of the linseed oil occurred over a period of 16 weeks for the samples encapsulated in zein/lauric acid without or with calcium citrate added (Figure 2). Linseed oil encapsulated in gelatin was rapidly degraded in the first 3 weeks.

In addition, encapsulated linseed oil was mixed in a hydrogel to simulate a food product with high water content. Two different hydrogels were used, one with low ionic strength and one with high ionic strength (1M NaCl). Again, stability of the linseed oil was monitored by FTIR spectroscopy. It was found that at room temperature no significant degradation of the linseed oil occurred for at least 10 weeks in the gel with low ionic strength and at least 7 weeks in the gel with high ionic strength (Figure 3). The effects were similar for samples with and without calcium citrate nanoparticles in the zein/lauric acid shell material.

When storing the hydrogels at elevated temperature, a clear difference was found for the samples without and with calcium citrate in the shell material. Over a period of 6 weeks, good stability of the linseed oil was found for the samples

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encapsulated in zein/lauric acid with 21w% dispersed calcium citrate, whereas samples encapsulated in zein/lauric acid without calcium citrate were fully degraded after 2–3 weeks (Figure 4).

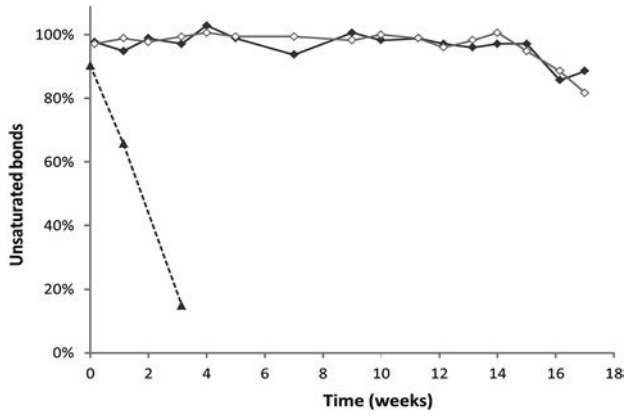

Figure 2. *Stability of encapsulated linseed oil in humid air (90% rh) at room temperature. Closed symbols: zein matrix; open symbols: zein matrix with calcium citrate nanoparticles; and dashed line: gelatin matrix.*

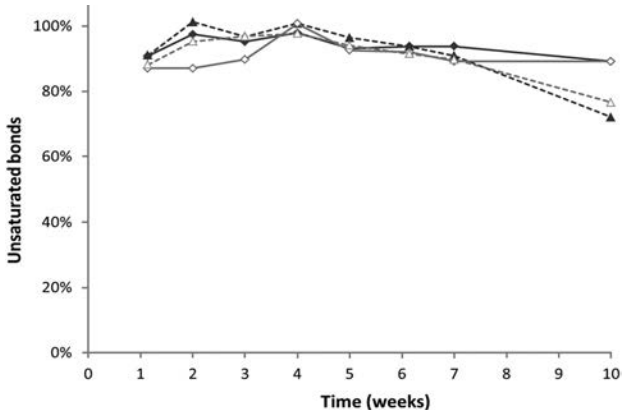

Figure 3. *Stability of encapsulated linseed oil in hydrogel matrix at room temperature. Closed symbols: zein matrix; open symbols: zein matrix with calcium citrate nanoparticles; solid lines: no NaCl; and dashed lines: 1M NaCl added to gel.*

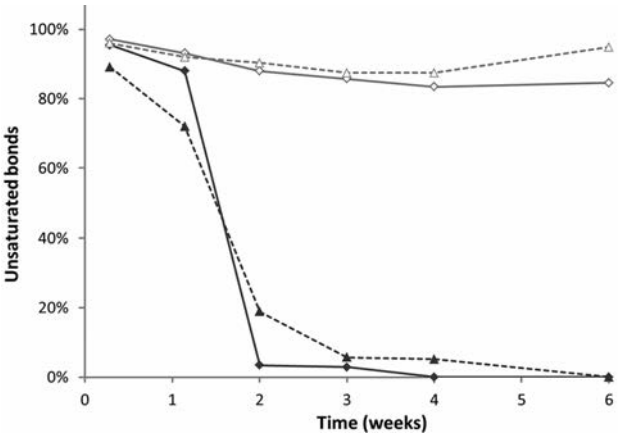

Figure 4. *Stability of encapsulated linseed oil in hydrogel matrix at 40°C. Closed symbols: zein matrix; open symbols: zein matrix with calcium citrate nanoparticles; solid lines: no NaCl; and dashed lines: 1M NaCl added to gel.*

Conclusions

Linseed oil could sufficiently be protected against oxidative degradation by encapsulation in zein/lauric acid shell material for a period of at least 16 weeks of storage in high relative humidity, or at least 7–10 weeks when present in a hydrogel. Increased stability at elevated temperature was obtained by addition of crystalline calcium citrate nanoparticles in the shell material. This approach, based on edible materials, may be a promising one for protection of oxygen-sensitive ingredients in food products with high water content.

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Announcement: Exciting New Expert Panel Initiative Within the Preclinical Sciences & Animal Health (PSAH) Division of CRS

Marilyn N. Martinez,[1] Chair, and Peter Cheifetz,[2] Deputy Chair, PSAH Division[3]

Introduction

The modern use of animal models for human anatomy and pathophysiology dates back to Claude Bernard in the 19th century, who considered it appropriate to take a reductionist approach to medical science (i.e., that complex systems are nothing but the sum of their parts).[1] Dr. Bernard also believed that if variable *X* caused response *Y* in one species, it would likewise cause response *Y* in humans. This belief was based upon his view that organs and other tissues are interchangeable between species, with the fundamental difference being attributed to allometry.

Although Dr. Bernard's perspective on the utility of animal models continues to hold true, there is a growing body of information on interspecies differences that must be considered. Whether extrapolating from animal to human, animal to animal, or human to animal, it is important to identify factors that can influence the accuracy of the interspecies predictions when used to support drug and drug product development. For example, inter- and intraspecies diversity often leads to failure to predict drug pharmacokinetics and pharmacodynamics when based strictly on relative body weights. Rather, the genetic and physiological complexity of humans and animals needs to be appreciated. For this reason, as stated by Francis Collins, director of the National Institutes of Health, "about half of the drugs that work in animals may turn out to be toxic for people, and some drugs may in fact work in people even if they fail in animals, meaning potentially important medicines could be rejected."[2]

Even in terms of percent oral bioavailability, the interspecies variability between rodents, dogs, and primates renders the relationship to human bioavailability as random scatter.[3] For example, differences in site-specific drug metabolism are known to occur across animal species. Esterase activity, although present in the order of duodenum ≥ jejunum ≥ ileum ≥ colon, is greater in rats compared with pigs and humans. The esterase activity of humans is somewhat greater than that of swine.[4] Other reviews of interspecies differences can be found elsewhere.[5–10]

With this in mind, whether a formulation is being developed for use in an animal species or whether the animal species is being used to predict product performance in humans, the multitude of variables impacting *in vivo* product performance need to be carefully understood. In this regard, interspecies extrapolation to support veterinary uses (e.g., cat, dog, horse, cattle, or sheep) should proceed with caution because of interspecies metabolic differences and differences in gastrointestinal physiology (or factors influencing parenteral drug absorption). For example, in their 2007 World Small Animal Veterinary Association presentation, "A Cat Is Not a Dog: Specific Therapeutic Considerations," Lefebvre and Reynolds discussed pharmacokinetic and bioavailability differences between dogs and cats that can lead to marked differences in appropriate dose/dosage regimens.[11]

An excellent resource for examining inter- and intraspecies differences that can influence drug pharmacokinetics can be found at www.interspeciesinfo.com. San José State University has a useful website on which the lifespan, heart rate, blood pressure, and lifetime heartbeats are compared across species (including humans): www.sjsu.edu/faculty/watkins/longevity.htm.

Exploring the relationship among physiology and drug pharmacokinetics and formulation effects is extremely complex, even when considering only a single species (e.g., humans). Not surprisingly, this complexity is amplified when applied to an array of animal species (as the recipient), when trying to use data from one animal species to predict product performance in a second animal species, or when using the animal as a model for human drug product development. This is one reason why the PSAH Division of CRS is an invaluable asset for formulators, regulators, practitioners, and industry. (To find the PSAH Division website, go to the CRS homepage and look under Community to see divisions and focus groups.) The PSAH Division is a multidisciplinary, international group of CRS members dedicated to advancing science and technology

1 FDA Center for Veterinary Medicine, Rockville, MD, U.S.A.
2 Formulation Development, Merial Limited (A Sanofi Company), North Brunswick, NJ, U.S.A.
3 Statements included in this manuscript reflect the opinion of the authors and should not be construed as representing the opinion of the U.S. Food and Drug Administration or Merial Limited (A Sanofi Company).

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in the field of controlled release relating to preclinical sciences and animal health. The mission of the division is

- to foster opportunities for collaboration between CRS members interested in animal and human health;
- to provide a platform to explore the use of animal models in preclinical studies, interspecies differences in drug absorption, pharmacokinetics, and target site drug delivery, and all matters relating to the animal health industry.

Thus, the PSAH Division is developing an initiative to engage the entire CRS membership to engage in focused discussions and to provide other mechanisms for exploring specific questions involving the animal as either the target species or as a preclinical model for human drug development.

The Initiative

The initiative will commence with development of a brief article in this publication, authored by an expert panel, covering a variety of subjects. From there, the panel will decide on any future activities related to these topics.

Examples of topics that may be of interest:

- interspecies differences in factors influencing drug absorption (oral and/or parenteral)
- the influence of species-specific needs on product formulation/drug delivery systems
- the impact of genetic variations on animal model selection
- *in silico* models for predicting interspecies differences
- influence of species' physiology/disease expression on site-specific drug delivery
- drug delivery systems and their use in animals or animal models

Our expectation is that the wealth of experience and knowledge within CRS will allow for a significant expansion of the list of potential topics to be considered.

This information will also be posted on our website under the resources section. Please visit the website for updates on the results of the initiative.

Conclusion

If you would like to share a topic, even if you yourself are not in a position to chair a group, please send the information to Megan Pagel, CRS Program Manager, at mpagel@scisoc.org. If the Division appeals to you, please join PSAH next time you renew your CRS membership, and think about joining the PSAH Committee. If you are interested, please email Megan Pagel.

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2014 CRS Elections: Cast Your Ballot

The 2014 CRS Elections will open in mid-May, and all members are encouraged to vote. Following the call for nominations that was sent to the membership in December, 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, Christopher McDaniel will take the position of Treasurer-Elect. At press time, the petition period for the BSA was still open. Electronic ballots will be sent to all eligible voting members of CRS in May, 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 2014 CRS Annual Meeting.

CRS Board

President-Elect

Debra Bingham,
Valeo Partners, U.S.A.

Marcus Brewster,
Johnson & Johnson, Belgium

Treasurer-Elect

Christopher McDaniel, U.S.A.

Secretary

Christine Allen,
University of Toronto, Canada

Padma Devarajan, Institute of
Chemical Technology, India

Director-at-Large (one open position)

Ben Boyd, Monash
University, Australia

James Oxley, Southwest
Research Institute, U.S.A.

Board of Scientific Advisors

In addition to the CRS Board positions, the membership will also vote on the three 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. Here are the candidates for BSA:

Marcel Bally, British
Columbia Cancer Research
Centre, Canada

Charles (Chuck) Frey,
Coating Place Inc.,
U.S.A.

Hamid Ghandehari,
University of Utah,
U.S.A.

Ick Chan Kwon,
KIST, Korea

Suzie Pun, University of
Washington, U.S.A.

Ruth Schmid, as the previous CRS Secretary, will oversee the 2014 election because of Debra Bingham, current CRS Secretary, being on the ballot. Any questions related to the election should be directed to Dr. Schmid, ruth.b.schmid@sintef.no.

Drug Delivery and Translational Research Update

Vinod Labhasetwar, Editor-in-Chief

Welcome to New *DDTR* Editorial Board Members

V. Prasad Shastri

Ben Boyd

As much as possible, we wish to have global representation on the editorial team of *DDTR*. To fill the gap, we have included two new members: Prof. V. Prasad Shastri of the University of Freiburg, Germany, and Prof. Ben Boyd of Monash University, Australia. We did not have representation on the editorial team from these countries. The new editorial board members are accomplished scientists in the field of drug delivery and have contributed significantly to *DDTR*. Prof. Shastri guest edited the *DDTR* special issue on regenerative medicine and chaired the *DDTR* best research paper award committee. Prof. Boyd also guest edited a *DDTR* special issue based on the Drug Delivery Australia 2012 symposium, which will be published soon.

New Article Type: Clinical Research

We have seen an increasing number of articles submitted to *DDTR* that involve human subjects but are not clinical trials. To address this issue, we have created a new article type, Clinical Research. This is in addition to the previous article type Clinical Trials. In upcoming issues, we will see papers reporting clinical research and clinical trials in drug delivery science and technology.

Recent Articles on Clinical Research and Clinical Trials

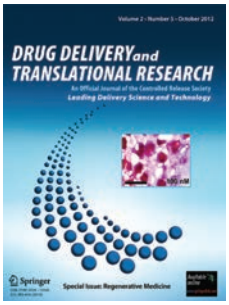
- "Nanomedicine for Glaucoma: Sustained Release Latanoprost Offers a New Therapeutic Option with Substantial Benefits over Eyedrops," by Tina T. Wong, Gary D. Novack, Jayaganesh V. Natarajan, Ching Lin Ho, Hla M. Htoon, and Subbu S. Venkatraman
- "Pharmacokinetics of Ketorolac Tromethamine Compression-Coated Tablets for Colon Delivery," by Sateesh Kumar Vemula, Prabhakar Reddy Veerareddy, and Venkat Ratnam Devadasu
- "First in Man Bioavailability and Tolerability Studies of a Silica–Lipid Hybrid (Lipoceramic) Formulation: A Phase I Study with Ibuprofen," by Angel Tan, Nasrin Ghouchi Eskandar, Shasha Rao, and Clive A. Prestidge
- "Profiling of Circulating MicroRNAs for Prostate Cancer Biomarker Discovery," by Christa Haldrup, Nobuyoshi Kosaka, Takahiro Ochiya, Michael Borre, Soren Høyer, Torben F. Orntoft, and Karina D. Sorensen

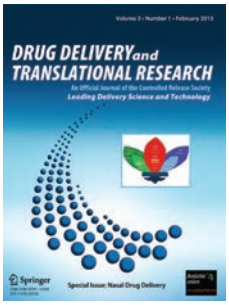
DDTR Outstanding Research Paper Award

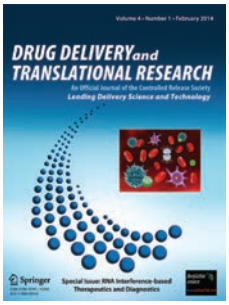
Consider submitting your best research for the 2014 *DDTR* Outstanding Research Paper Award. The paper will be selected by the committee from research articles published in *DDTR* during 2014. The award will be presented during the 42nd CRS annual meeting, to be held July 26–29, 2015, at Edinburgh International Conference Centre, Edinburgh, Scotland. Visit controlledreleasesociety.org for award criteria.

DDTR Special Issues

DDTR has published several high-impact special issues on drug delivery and translational research. If you are interested in developing a special issue, please contact me (labhasv@ccf.org) with a brief outline. CRS members have free access to these issues as membership benefit.







Advances in Vaginal Drug Delivery: Volume 1, Issue 3, June 2011, edited by David R. Friend

Advances in Image-Guided Drug Delivery: Volume 2, Issue 1, February 2012, edited by Arash Hatefi and Tamara Minko

Drug Delivery to the CNS: Volume 2, Issue 3, June 2012, edited by Pericles Calias

Regenerative Medicine: Volume 2, Issue 5, October 2012, edited by V. Prasad Shastri

Nasal Drug Delivery: Volume 3, Issue 1, February 2013, edited by Elka Touitou and Lisbeth Illum

Cancer Stem Cells: Volume 3, Issue 2, April 2013, edited by Jayanth Panyam

NanoBio Interface: Volume 3, Issue 4, August 2013, edited by Subhra Mohapatra, Srinivas Nagaraj, and Shyam S. Mohapatra

Nanomedicine: Prospects and Challenges: Volume 3, Issue 5, October 2013, edited by Padma Devarajan and Vandana Patravale

RNA Interference-Based Therapeutics and Diagnostics: Volume 4, Issue 1, February 2014, edited by Dan Peer and Ken Howard ■

NZCRS Symposium at Australasian Conference

Andrew McLaughlin and Arlene McDowell
School of Pharmacy, University of Otago, New Zealand

The 2013 annual Australasian Pharmaceutical Science Association (APSA) conference was held at the Hunter Centre, University of Otago, Dunedin, New Zealand, on December 8–11. The New Zealand Local Chapter of the Controlled Release Society (NZCRS) was pleased to organise a one-day symposium as part of the APSA program. The symposium included invited and contributed speakers from as far afield as the United States, Denmark, China, and of course New Zealand.

Session one was themed "The Biological Therapeutic Interface" and commenced with keynote speaker Prof. Peter Swaan from the University of Maryland, Baltimore, U.S.A., with a presentation titled "Good Cop, Bad Cop: Intracellular Trafficking and Its Implications for Drug Targeting," which highlighted the transport of macromolecules into cells via endocytosis and how to target this process to achieve highly specific drug delivery. Prof. Thomas Rades from the University of Copenhagen, Denmark, was an invited speaker to the symposium. He spoke about "Preclinical Formulation of Therapeutics—What Does Industry Want?" This talk outlined the need to increase drug solubility of class II drugs by using various techniques to transform the structure of drugs in formulations from crystalline to amorphous, thus increasing the dissolution of drugs and therefore increasing their bioavailability.

Speakers at the NZCRS symposium enjoying the conference dinner. Left to right: Jonathan Bray, Sarah Hook, NZCRS keynote speaker Peter Swaan, Natalie Medlicott, NZCRS president Arlene McDowell, Thomas Rades, Chandima Hettiarachchi, and Simon Young. Photo by Seen in Dunedin.

Conference participants investigating the material available at the NZCRS display table (left to right: Katrin Kramer, Bettina Poller, and Himang Mujoo). Photo by Arlene McDowell.

Carrying on with this theme, Prof. Yuan Huang (Sichuan University, China) talked about the mucus layer as a barrier to drug delivery and demonstrated that TMC-CSK modified nanoparticles had higher uptake across the Caco-2/HT29-MTX cell monolayer compared with unmodified nanoparticles. Following on with nanoparticles, Dr. Arlene McDowell (University of Otago, New Zealand) discussed how cell-penetrating peptides can be used to increase drug bioavailability. Using a histidine tagging method, arginine-tagged nanoparticles showed increased uptake compared with untagged nanoparticles. Assoc. Prof. Natalie Medlicott (University of Otago, New Zealand) introduced the audience to the hydrophobic interface and how proteins (in particular globular proteins) interact with this interface. She described how interfacial rheology can be used as a tool to investigate protein aggregation at the interface. The session closed with CRS president Prof. Ian Tucker (University of Otago, New Zealand), who gave a comprehensive overview of mastitis in dairy cows and the challenges involved in delivering an antibiotic to the site of infection. He also discussed the translation of the delivery methods to effective products for treatment.

The second session, themed "Progressing Ideas to the Clinic," opened with Prof. Ami Radunskaya (Claremont Colleges,

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U.S.A.), who introduced us to mathematic modelling, in particular a compartmental model of liposomes and the effect that bile salt concentration has on permeability. She also described a model for drug release from a controlled release tablet and how best to determine the correct conditions for the desired release rate. Dr. Shakila Rizwan (University of Otago) gave a presentation on zebrafish and convinced the audience that zebrafish can be used as an alternative to other animal models for the study of drugs. Assoc. Prof. Jonathan Bray (Massey University, New Zealand) gave an interesting talk about cancer in canines and the similarities between human and canine soft tissue sarcoma. He described how a canine cancer model can be used for verification of drug delivery mechanisms in phase I trials.

"Advances in Delivery of Cancer Therapeutics" was the theme for the final session. Prof. Sarah Hook (University of Otago, New Zealand) talked about antibody-directed prodrug therapy (ADEPT). This idea uses a nanoparticle to codeliver a prodrug and activating enzyme. It is a pH-responsive system in which a ligand binds to a receptor, the pH breaks down the nanoparticle, and the enzyme activates the prodrug. She also talked about a vaccine for melanoma in which an antigen was encapsulated within a liposome; the adjuvant used was α-galactosylceramide. Because the liposome was cationic it was found to have better loading of antigen. Dr. Kahled Greish (University of Otago, New Zealand) followed with selective tumour targeting using nanomicelles for the treatment of prostate cancer. Hayley Nehoff (Ph.D. candidate, University of Otago, New Zealand) also spoke of micelles for use in cancer therapy. She described how incorporating two tyrosine kinase inhibitors into a micelle showed cytotoxicity *in vitro*, and styrene maleic acid micelles improved pharmacokinetics.

A great conclusion to the day was the enjoyable conference dinner held at New Zealand's only castle, Larnach Castle, located on the beautiful Otago Peninsula.

The NZCRS symposium was of high quality and very informative, with the hope of new collaborations stemming from it. The symposium complemented the ASPA conference well, and we thank everyone involved. ■

Dunedin is known as the "Edinburgh of the South," and delegates were welcomed to the conference dinner at Larnach Castle by a bagpiper. Photo by Seen in Dunedin.

Welcome New CRS Members

Srinivas Abbina
Nadia Abed
Yasmin Mohamed Abdalla Abo-zeid
Khuloud T. Al-Jamal
Mohamad-Gabriel Alameh
Amjad Alhalaweh
Siddique Akber Ansari
Danny Brown
David S. Collins
Inayet Ellis
Renea Faulknor
Nadège Grabowski
Naim A. Hage
Mirza Akram Hossain
Marie-Eve Leclaire
Serom Lee
So Jin Lee
Franziska Leifer
Panagiotis Mastorakos
Sara Movassaghian
Amol Naringrekar
Christopher E. Nelson
Roger H. Pak
Rishi Paliwal
Hongchun Qiu
Mazda Rad Malekshahi
Farshad Ramazani
Robert A. Reed
Gaurav Sahay
Giuseppina Salzano
Can Sarisozen
Luana Sasso
Phei Er Saw
Dmitri Simberg
Meghna Talekar
Ashkan Tavakoli Naeini
Daniel Veilleux
Yang Yang
Zheng Zhang
Qi Zhang

CRS Leading Delivery Science and Technology

People in the News

Compiled by Steven Giannos, Independent Consultant

InVivo Therapeutics Names Thomas R. Ulich, M.D., as Its New Chief Scientific Officer

Business Wire: February 24, 2014 – CAMBRIDGE, MA, U.S.A. – InVivo Therapeutics Holdings Corp. (NVIV) today announced appointment of Thomas R. Ulich, M.D., as chief scientific officer, effective February 24, 2014.

Dr. Ulich previously served as executive vice-president of research and development of ConjuChem Biotechnologies from 2006 to 2010. Prior to that, he served as senior vice-president of research and development for Alnylam Pharmaceuticals from 2003 to 2004. Before that he served at Amgen as vice-president of preclinical development from 1993 to 2001 and as vice-president of preclinical development and protein therapeutics from 2001 to 2003. Dr. Ulich has a B.A. from Dartmouth College and an M.D. from UCLA Medical School. He has medical board certification from the American Board of Anatomic Pathology, the American Board of Clinical Pathology, and the American Board of Immunopathology.

Mark Perrin, InVivo's chief executive officer, said, "Tom Ulich brings to InVivo a broad scientific background and expertise that will be invaluable as we build our biomaterials portfolio."

InVivo Therapeutics Holdings Corp. is a pioneering biomaterials company with unique technologies for drug delivery with a focus on treatment of spinal cord injuries. The company was founded in 2005 with proprietary technology co-invented by Robert Langer, Sc.D., professor at Massachusetts Institute of Technology, and Joseph P. Vacanti, M.D., who is affiliated with Massachusetts General Hospital. In 2011 the company earned the David S. Apple Award from the American Spinal Injury Association for its outstanding contribution to spinal cord injury medicine. The publicly traded company is headquartered in Cambridge, Massachusetts. For more details, visit, www.invivotherapeutics.com.

Sonrgy Announces Key Management Recruits

Business Wire: February 13, 2014 – SAN DIEGO, CA, U.S.A. – Sonrgy, Inc., a biotechnology company developing focused drug delivery technologies, has announced the appointment of key executives.

Brian O'Callaghan has been appointed as the company's chairman and CEO. Mr. O'Callaghan was most recently the CEO at Sangart, Inc., a San Diego-based pharmaceutical company. He brings 25 years of senior management experience in the life science sector, with companies that include NPS Pharmaceuticals, Covance, Novartis, BioPartners (cofounder), Merck, Pfizer, and Bayer. Mr. O'Callaghan holds an M.B.A. from Henley College of Business Management in the United Kingdom and a marketing diploma from Cork Institute of Technology and Marketing Institute of Ireland.

In addition, David Renas is joining Sonrgy as chief financial officer. Mr. Renas has a background in finance and law, having served as CFO and general counsel at Sangart, as an attorney in private practice with Gray Cary Ware & Freidenrich (now DLA Piper) and Foley & Lardner, and as a CPA at Deloitte. Mr. Renas holds a bachelor of arts degree in economics from Stanford University and a juris doctorate from the University of California at Davis.

These key recruits are aimed at helping the company execute on developing its first clinical drug candidate using Sonrgy's proprietary SonRx delivery platform.

"I am delighted to join Sonrgy. This is a very promising technology with a real opportunity to address the need for precise drug delivery, particularly in the oncology space," said Brian O'Callaghan. "I look forward to working with the founders to bring the SonRx technology to the clinic."

Sonrgy is a preclinical stage biotechnology company based in San Diego, California, that is developing a targeted chemotherapy delivery platform to improve survival and quality of life for millions of cancer patients. Sonrgy's tiny nanocarriers safely transport potent chemotherapy drugs to cancer tumors and release high doses on command in response to a focused beam of ultrasound. These carriers deposit drugs directly at the tumor cell sites, in order to avoid the many serious side effects of toxic chemotherapy circulating in the blood stream. Nanocarriers can deliver chemotherapy before surgery to reduce tumor size, after surgery to prevent recurrence, and in situations when surgery is not possible to arrest tumor growth. This distinctive approach to delivering chemotherapy can be applied to many cancer tumors and enables more intensive treatment of the cancer, potentially improving effectiveness while reducing harmful effects on the rest of the body.

Alliqua Appoints Janice M. Smiell, M.D., as Its First Chief Medical Officer

Business Wire: February 10, 2014 – LANGHORNE, PA, U.S.A. – Alliqua, Inc. (NASDAQ: ALQA) ("Alliqua" or "the company") has appointed Janice M. Smiell, M.D., as its chief medical officer, a newly created position.

Dr. Smiell has more than two decades of experience in clinical trial design, clinical development and planning, and clinical regulatory submissions. In practice as a general surgeon, she has specialized in wound healing, wound care, and trauma. Most

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recently, she was an independent consultant in drug, device, tissue, and cells clinical development planning, as well as medical monitoring and management. Prior to this, she served as VP of medical affairs at LifeCell Corporation, where she established the clinical operations, biometrics, and safety departments. Earlier, as executive director of clinical R&D at Celgene Corporation, she initially led the clinical development of biomaterials and stem cells and subsequently oversaw research teams developing immune modulators in several indications. She also served in various positions of increasing responsibility at The R.W. Johnson Pharmaceutical Research Institute, including senior director, global clinical R&D. Prior to this, she served as medical director of the Wound Care Center at Morristown Memorial Hospital. She holds an M.D. degree from the Medical College of Pennsylvania.

Dr. Smiell said, "As a veteran of the wound healing and wound care space, I am acutely aware of the need for significant innovation in this area. I am extremely enthusiastic about Alliqua's vision of offering a suite of products that target a broad spectrum of wound conditions. I am greatly looking forward to working with Alliqua's management team to help evaluate new technologies and expand the company's portfolio to address diverse wound care needs, as well as to coordinate our clinical trials."

David Johnson, chief executive officer of Alliqua, said, "Dr. Janice Smiell brings a tremendous amount of management and clinical experience to Alliqua, and we are honored to have her serve as our chief medical officer. In an era in which the wound care space is evolving faster than ever, it is imperative that we have top-notch guidance to navigate the scientific, technical, and regulatory milestones ahead of us. I am confident that Dr. Smiell, as Alliqua's first chief medical officer, is the ideal person to assist us in these efforts over the coming years as we grow our wound care product portfolio."

Alliqua, Inc. (ALQAD) ("Alliqua") is a biopharmaceutical company focused on the development, manufacturing, and distribution of proprietary transdermal wound care and drug delivery technologies. Alliqua's technology platform produces hydrogels, a three-dimensional cross-linked network of water-soluble polymers capable of numerous chemical configurations.

Alliqua currently markets its line of 510(k) FDA-approved hydrogel products for wound care under the SilverSeal® brand, as well as the sorbion sachet S and sorbion sana wound care products. Alliqua's electron beam production process, located at its 16,000 square foot GMP manufacturing facility in Langhorne, Pennsylvania, allows Alliqua to develop and custom manufacture a wide variety of hydrogels. Alliqua's hydrogels can be customized for various transdermal applications to address market opportunities in the treatment of wounds as well as the delivery of numerous drugs or other agents for pharmaceutical and cosmetic industries. Additionally, Alliqua's drug delivery platform, in combination with certain active pharmaceutical ingredients, can provide pharmaceutical companies with a transdermal technology to enhance patient compliance and potentially extend the patent life of valuable drug franchises. ■

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In the News

Compiled by Steven Giannos, Independent Consultant

March

Mallinckrodt Receives FDA Approval for XARTEMIS XR (Oxycodone Hydrochloride and Acetaminophen) Extended-Release Tablets (CII)

Business Wire: March 12, 2014 – DUBLIN, Ireland – Mallinckrodt plc (NYSE: MNK) today announced that the U.S. Food and Drug Administration (FDA) has approved XARTEMIS™ XR (oxycodone hydrochloride and acetaminophen) extended-release tablets (CII), previously known as MNK-795, for the management of acute pain severe enough to require opioid treatment and in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would otherwise be inadequate. XARTEMIS XR is the first and only extended-release oral combination of two clinically proven pain medications—oxycodone and acetaminophen.

XARTEMIS XR has both immediate- and extended-release components: formulated to provide onset of pain relief in less than one hour and to allow twice-daily dosing. The product's release profile combines Mallinckrodt's newly patented technology, including design, formulation, pharmacokinetic, and release characteristics, and Depomed's advanced Acuform® drug delivery technology.

The approval is based, in part, on the pivotal phase 3 efficacy study conducted in an acute postsurgical pain model. XARTEMIS XR met the study's primary endpoint and showed statistically significant improvement in pain scores compared with placebo from baseline over 48 hours.

In addition to the efficacy study, Mallinckrodt conducted extensive lab testing and a human abuse liability study with XARTEMIS XR. Data from Mallinckrodt's studies related to the product were described in 15 scientific presentations at PAINWeek, held September 4–7, 2013. While the approved label for XARTEMIS XR does not include abuse-deterrent language, Mallinckrodt will continue working closely with the FDA to develop more data to characterize abuse-deterrence features of XARTEMIS XR and other products utilizing this technology platform. The company is conducting additional studies and will be providing additional data in the near future.

Pain that is uncontrolled or unmanaged results in ongoing and very significant costs to U.S. businesses in terms of lost productivity. In 2010, there were over 102 million surgical procedures ordered or performed at office visits. That same year, there were 51 million inpatient surgeries performed. The Institute of Medicine reported in 2011 that 80% of patients undergoing surgery experience postoperative pain. Of these, 88% report the pain is moderate, severe, or extreme.

"Acute pain doesn't last for only four to six hours, and neither should its treatment. With the extended-release profile of XARTEMIS XR, patients may not need to wake in the night to take a dose," said Nathaniel Katz, M.D., M.S., adjunct assistant professor of anesthesia at Tufts University School of Medicine. "A long-acting combination analgesic that can effectively deliver oxycodone and acetaminophen for acute pain patients experiencing pain throughout the day and night is a welcome addition to the treatment landscape."

"The FDA approval of XARTEMIS XR exemplifies Mallinckrodt's dedication to developing and providing new treatment options for people with pain," said Mark Trudeau, president and chief executive officer of Mallinckrodt. "Mallinckrodt remains committed to continuing its work to develop innovative formulations for our product lines to help ensure access to appropriate pain treatment for the millions of patients suffering from acute pain, and we will continue to work closely with the FDA as we engage in further development programs for XARTEMIS XR and other products utilizing this technology platform."

Mallinckrodt is dedicated to providing quality medications for treatment of patients with pain and equally committed to fighting the problems of opioid misuse and abuse. The company supports a broad range of programs that encourage and support only appropriate use of pain medications, and we address diversion and abuse through a multidimensional approach that includes educational efforts, monitoring for suspicious orders of controlled substances, drug take-back programs, and research into abuse-deterrent technologies.

Evonik Reaches Milestone with Permanently Implantable VESTAKEEP® PEEK

Business Wire: March 10, 2014 – PARSIPPANY, NJ, U.S.A. – Evonik Corporation said today each of its primary implantable VESTAKEEP® PEEK product lines have been referenced in customer products that have received U.S. Food and Drug Administration's (FDA) 510(k) clearance for permanent implant use.

"We are excited about the growing interest VESTAKEEP® PEEK is receiving within the medical device industry," said Peter Colburn, director of Evonik's VESTAKEEP® implant product lines. "It is clear that medical device manufacturers need innovative companies like Evonik to create materials and offer services meeting their specific needs. VESTAKEEP® PEEK is known for its superior biocompatibility, biostability, and combination of stiffness and ductility, making it not only a unique polymer but also an excellent material for medical implant applications."

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The product lines used in medical devices that have received FDA 510(k) clearance include VESTAKEEP® i2G resin for injection molding applications, VESTAKEEP® i4G resin for injection molding and extrusion applications, and VESTAKEEP® i4R stock shape for machined implant applications.

"We are building a global business around the needs of the marketplace," said Sanjeev Taneja, global vice president of Evonik's VESTAKEEP® product lines. "Momentum is building as we develop the next generation of PEEK product lines through Evonik's vast global research and development resources and network of the world's leading research institutions. Currently, we are developing numerous devices for cardiovascular, neuromodulation, sleep apnea, and dental applications."

Products using VESTAKEEP® PEEK that have already received FDA 510(k) clearance cover a broad range of applications including spinal implants, suture anchors, cranial implants, pharmaceutical drug delivery devices, and implantable MRI markers supporting image-guided cancer treatment procedures.

Colburn cites the VESTAKEEP® PEEK Masterfile strength as a key contributing factor to the material's success within the medical device market. Several VESTAKEEP® PEEK products are in development and planned for launch this year including VESTAKEEP® PEEK with barium sulfate ($BaSO_4$) and VESTAKEEP® PEEK with carbon fiber (CFF).

Catalent Announces Agreement for One of the First Regenerative Therapies to Employ iPS Cells in Humans with CiRA, Kyoto University

Business Wire: March 10, 2014 – SOMERSET, NJ, U.S.A. – Catalent Pharma Solutions, the global leader in advanced delivery technologies and development solutions for drug, biologic, and consumer health products, today announced an agreement with the Center for iPS Cell Research and Application (CiRA) at Kyoto University in Japan to make a major advancement toward one of the first regenerative human therapies with induced pluripotent stem (iPS) cells applicable to humans. Under this agreement, Catalent manufactures an anti-CORIN monoclonal antibody using its proprietary GPEx® cell line expression technology for a planned clinical research project to develop an iPS cell-based transplant therapy for Parkinson's disease at CiRA, which is directed by Prof. Dr. Shinya Yamanaka, the joint winner of the Nobel Prize in Physiology or Medicine in 2012 for "the discovery that mature cells can be reprogrammed to become pluripotent."

The anti-CORIN monoclonal antibody was discovered and developed through collaborative research between CiRA and KAN Research Institute, Inc., a research subsidiary of a major Japanese pharmaceutical company, Eisai Co., Ltd. (www.kan-research.co.jp/english/index.html). Catalent has already engineered cell lines producing the anti-CORIN monoclonal antibody for CiRA using their GPEx technology, and the antibody has been shown to be useful for sorting CORIN-expressing cells in *in vitro* studies at CiRA. Under the agreement, Catalent will conduct further clonal selection and manufacturing of the monoclonal antibody under a properly conditioned environment for CiRA, which will use the antibody to select dopaminergic neurons derived from iPS cells and plans to transplant the selected cells into patients in a possible clinical research program upon receipt of regulatory approval. Catalent will also support CiRA with formulation, production, and sterile fill/finish of the monoclonal antibody, aspects of the project that could not be handled within academia.

"It is a great honor to work with a team led by world-renowned Prof. Dr. Jun Takahashi," commented Shingo Nakamura, Catalent's director of biologics, Japan. "We are very excited to help accelerate the development of a unique regenerative therapy using our GPEx technology and look forward to working with CiRA to bring better treatments to market faster."

Jonathan Arnold, vice president and general manager of Catalent Biologics, added, "We are witnessing an increased demand for biologics in the Asia Pacific market. Our GPEx technology, our expertise, and access to antibody drug conjugates, combined with our investment in state-of-the art manufacturing facilities, mean that we are ideally placed to act as a partner to CiRA in this exciting project."

Catalent's GPEx technology produces high-yielding, stable mammalian cell lines and has been successfully applied in the manufacture of more than 500 different recombinant proteins, over 30 of which are now undergoing clinical trials or being supplied commercially. Antibiotic selection and traditional gene amplification are not required when using GPEx technology, resulting in shorter clonal cell line development timelines.

Alfred Mann Foundation for Scientific Research Creates New Medical Device Firm

Business Wire: March 5, 2014 – VALENCIA, CA, U.S.A. – The Alfred Mann Foundation (AMF) is pleased to announce the creation of Medallion Therapeutics, Inc. The new entity is a life sciences company formed to provide targeted delivery solutions for pharmaceuticals and biologic therapies. Medallion Therapeutics has engaged industry veteran executives Chief Executive Officer Donald L. Deyo and Chief Commercial Officer Eric S. Harris to lead the team.

The Medallion Therapeutics product line is based on a novel implantable drug delivery infusion pump developed by AMF scientists and engineers to provide superior safety, connectivity, and large molecule infusion capabilities. These capabilities address both the requirements of currently approved clinical indications, as well as enable future expansion into new indications in areas such as diabetes and neurodegenerative disease. Medallion Therapeutics is the result of over 10 years of research and development to create the novel Medallion implantable drug delivery system. The company is currently conducting a pivotal clinical evaluation in the United States to

support an upcoming submission for premarket approval (PMA), as well as pursuing CE Mark certification to support distribution in Europe.

Founded in 1985 by healthcare entrepreneur Alfred E. Mann, AMF has developed and commercialized several medical devices, benefiting thousands of patients across the globe. The formation of the new venture reflects the strategy of AMF to develop innovative solutions to major unmet medical needs and create companies to commercialize the innovation once mature. David Hankin, chief executive officer of the Alfred Mann Foundation, comments: "The Medallion Therapeutics pump holds the promise of providing patients and physicians with a superior method of infusion therapy than current market alternatives. Don Deyo, Eric Harris, and the group of AMF professionals joining Medallion Therapeutics constitute a world-class team that will bring this innovative solution to patients around the globe."

Don Deyo noted, "The AMF engineers have created a tremendous platform that addresses major needs associated with currently marketed implantable delivery devices, as well as opens the door to targeted delivery of large molecules associated with novel biologic therapies for neurodegenerative diseases. Our U.S. clinical study is moving rapidly toward achieving the enrollment required for PMA submission. The Medallion Therapeutics team is working diligently to bring our superior, cost-effective, targeted delivery solutions to physicians and patients around the world."

Eric Harris stated, "There is tremendous need for the innovative infusion, safety, and connectivity capabilities of the Medallion system in all established indications. I look forward to building upon the experience of our leadership team in this market to earn the confidence of clinicians around the world for our innovative solutions for their patients."

Teva Launches ADASUVE® in the United States

Business Wire: March 3, 2014 – JERUSALEM, Israel – Teva Pharmaceutical Industries Ltd. (NYSE: TEVA) announced today the commercial launch of ADASUVE® (loxapine) inhalation powder 10 mg, the first and only orally inhaled medicine for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

ADASUVE® is administered through Alexza Pharmaceuticals' (NASDQ: ALXA) innovative proprietary Staccato® single-use, handheld drug delivery technology system. This new drug-device combination product provides rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine, a first-generation antipsychotic, to the lung. Administration of ADASUVE® results in rapid absorption of loxapine, with a maximum plasma concentration achieved in approximately 2 minutes.

Efficacy was demonstrated in two clinical trials in acute agitation: one in schizophrenia and one in bipolar I disorder. Patients receiving ADASUVE® experienced a statistically significant reduction in agitation at two hours, with an effect seen as early as 10 minutes postdose.

Due to the risk of bronchospasm that has the potential to lead to respiratory distress and respiratory arrest, ADASUVE® is contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD), or other pulmonary disease associated with bronchospasm and is only available through a restricted program called the ADASUVE® Risk Evaluation and Mitigation Strategy (REMS). ADASUVE® must be administered only in a REMS-enrolled healthcare facility that has immediate access onsite to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation).

"Existing treatment options for patients with agitation associated with schizophrenia or bipolar I disorder are limited to oral tablets or injectable modes of administration, sometimes requiring the use of restraints," said Richard Jaffe, M.D., Medical Director for Research and Clinical Trials at the Belmont Center for Comprehensive Treatment, Philadelphia, Pennsylvania, and a clinical trial investigator. "ADASUVE® is a drug-device combination that offers health care providers a new option to help manage agitation."

Patients experiencing agitation associated with schizophrenia or bipolar I disorder often manifest behaviors that interfere with their care, such as threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior that lead clinicians to use rapidly absorbed antipsychotic medications to help control the agitation quickly. Agitation associated with schizophrenia and bipolar I disorder is estimated to result in approximately 7 million episodes that end up in an acute emergency treatment setting each year. Acute agitation can increase in severity and escalate unpredictably.

"The availability of orally inhaled ADASUVE® provides a rapid onset of action that quickly improves symptoms for patients and gives providers in enrolled hospitals another treatment choice," said Michael McHugh, vice president and general manager, Teva Select Brands and Teva Women's Health. "As part of our ongoing commitment to enhancing patient care and bringing new therapies and delivery systems to the market that fit within our areas of expertise, Teva is pleased to launch this new treatment choice that is aligned with Teva's New Therapeutic Entities (NTE) program."

Two phase 3 short-term clinical efficacy trials demonstrated significant improvement in agitation at 2 hours in patients with schizophrenia or bipolar I disorder treated with ADASUVE®. These studies demonstrated a 49% reduction in agitation symptoms from baseline in schizophrenia patients, as compared with 33% in placebo, and 53% reduction in bipolar I patients, as compared with 27% in placebo. Improvement was rapidly

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achieved at 10 minutes postdose with a 19% reduction in agitation symptoms from baseline in schizophrenia patients and a 23% reduction in bipolar I patients, both as compared with 10% in placebo.

Please see additional important safety information including boxed warnings and REMS Program information below. The most common adverse reactions (greater than at least 2% in the treated group and greater than in the placebo group) in short-term, placebo-controlled trials were dysgeusia (abnormal taste), sedation, and throat irritation.

Teva licensed the U.S. commercial rights to ADASUVE® in May 2013 from Alexza Pharmaceuticals, inventor and developer of the Staccato® system and of ADASUVE®. Under the terms of the license and supply agreement, Teva is responsible for all U.S. commercial and clinical activities including U.S. postapproval clinical studies. Alexza is responsible for manufacturing and supplying ADASUVE® to Teva for commercial sales and clinical trials. ADASUVE® is currently available through a select distribution network. Please call (800) 292-4283 or visit www.adasuve.com for additional information.

February

Ocular Therapeutix Secures Reimbursement Code for Insertion of Drug-Eluting Intracanalicular Plugs

Business Wire: February 26, 2014 – BEDFORD, MA, U.S.A. – Ocular Therapeutix announces that the American Medical Association (AMA) CPT Editorial Panel recently approved a category III CPT code 0356T for the insertion of a drug-eluting implant, including punctal dilation and implant removal when performed, into the lacrimal canaliculus. The new category III CPT code, which is for emerging technologies, services, and procedures, is effective July 1, 2014. Ocular Therapeutix pursued approval of this code in conjunction with the American Academy of Ophthalmology and the American Optometric Association at the AMA CPT Panel meeting in October 2013.

Ocular Therapeutix is currently in clinical trials for dexamethasone intracanalicular plugs (OTX-DP) for the treatment of postoperative inflammation and pain and travoprost intracanalicular plugs (OTX-TP) for reduction of intraocular pressure in patients with glaucoma or ocular hypertension. The new code could be used in clinical trials to establish use and will provide a mechanism for reimbursement for insertion of these intracanalicular plugs, following Food and Drug Administration (FDA) approval.

"Obtaining the CPT code for insertion of our drug-eluting plugs is an important step in the reimbursement process as we begin planning for the introduction of our sustained drug delivery platform technology," stated Amar Sawhney, Ph.D., president and CEO of Ocular Therapeutix, Inc.

Ocular Therapeutix is developing the company's proprietary absorbable polyethylene glycol hydrogel intracanalicular plug technology to release drugs in a sustained fashion over a specified period of time depending on the drug and its corresponding therapeutic need. At the end of the treatment period, the plug is designed to absorb, and to exit the nasolacrimal system without need for removal by the physician. The plugs contain a visualization agent for retention monitoring throughout the treatment period.

Mallinckrodt Receives Patent from U.S. Patent and Trademark Office

Business Wire: February 25, 2014 – DUBLIN, Ireland – Mallinckrodt (NYSE: MNK) today announced that it was granted a patent from the U.S. Patent and Trademark Office, which contains composition claims directed to unique design, formulation, pharmacokinetic, and release characteristics of XARTEMIS™ XR. XARTEMIS XR (formerly known as MNK-795) is an investigational extended-release oral formulation of oxycodone and acetaminophen that has been studied with twice-daily dosing for the management of acute pain in a postsurgical model. If approved, XARTEMIS XR will be the first oxycodone and acetaminophen combination medication specifically designed with immediate- and extended-release components. The patent, U.S. patent number 8,658,631, was issued on February 25, 2014.

The release profile of XARTEMIS XR combines Mallinckrodt-proprietary technology and Depomed's advanced Acuform® drug delivery technology. Between the Mallinckrodt and Depomed patent families, Mallinckrodt believes XARTEMIS XR will have strong patent protection for its novel features.

"XARTEMIS XR, a key driver in our near-term pipeline, represents an important component of our strategy to unlock continued potential and grow our branded specialty pharmaceutical portfolio," said Mark Trudeau, president and chief executive officer, Mallinckrodt. "Mallinckrodt's patent, which includes the product's release profile, underscores our ability to effectively leverage our core formulation capabilities and partnerships."

Egalet Receives Fast Track Designation for Egalet-001 and Egalet-002 for Moderate to Severe Pain

PRNewswire: February 20, 2014 – WAYNE, PA, U.S.A. – Egalet Corporation (Nasdaq: EGLT) ("Egalet") today announced that the U.S. Food and Drug Administration (FDA) has granted Fast Track status for both Egalet-001, an abuse-deterrent, extended-release, oral morphine formulation, and Egalet-002, an abuse-deterrent, extended-release, oral oxycodone formulation, both in development for the treatment of moderate to severe pain.

FDA's Fast Track program facilitates the development of drugs intended to treat serious or life-threatening conditions and that have the potential to address unmet medical needs. A drug program with Fast Track status is afforded greater access to the FDA for the purpose of expediting the drug's development, review, and potential approval.

"Fast Track designation for Egalet-001 and Egalet-002 is an important step forward in the development of our two lead product candidates," said Bob Radie, Egalet's president and chief executive officer. "We look forward to working with the FDA and plan to submit the New Drug Application for Egalet-001 in the fourth quarter of this year."

With Fast Track status, sponsors can have more frequent and timely communications and meetings with the FDA regarding product development plans. The Fast Track designation may result in eligibility for priority review of New Drug Applications.

New Smoking Cessation Innovation Receives Grant from the National Institutes of Health

PRWEB: February 10, 2014 – CAMBRIDGE, MA, U.S.A. – The National Cancer Institute division of the NIH has recently awarded Chrono Therapeutics (CHRONO), a pioneer in digital drug products, a $2.23M grant to commercialize its lead product—SmartStop™. Smartstop is the first "smart" transdermal nicotine replacement therapy (NRT) system that synchronizes the delivery of nicotine at the times of cravings to prevent cravings from occurring. Smartstop is the lead product of the company's digital-health technology platform and is the first fusion of optimized NRT and individualized digital behavioral support.

The grant is the first time the NIH has issued an initial Fast Track phase I/phase II grant this large for a programmable NRT product. The recently awarded grant builds upon a 2012 grant from the NIH that supported initial *in vitro* testing, infrastructure, and product development. The additional grant will be used to conduct the final clinical trial.

"Receiving a grant award this large from a prestigious public health organization like the NIH validates our approach to address the serious epidemic that kills a half million Americans every year," commented Alan Levy, the new CEO and chairman of the board of Chrono Therapeutics.

SmartStop's wearable transdermal nicotine delivery system customizes nicotine replacement therapy dosage based on smoker's sleep-wake cycle, meals, and craving patterns. This new technology fills an unmet need in personalizing smoking cessation and ensuring compliance with therapy.
Key features include:

- Synchronization with cravings and delivery of the right amount of nicotine when smokers need it.
- Seamless connection via Bluetooth technology to all mobile devices.
- Automated optimal delivery.
- Digital behavior support.

Alan Levy was recently appointed CEO of Chrono Therapeutics. Alan joins Chrono from Incline Therapeutics and brings a stellar track record of success in leading multiple companies from development to successful commercialization. His prior positions include chief executive officer of Incline Therapeutics and chairman of the board of directors and CEO of Northstar Neuroscience, Inc., a company he cofounded. Levy also served as president and chief executive officer of Heartstream, Inc., and president of heart technology. Levy has a strong background in product development and commercialization from his tenure as a senior executive at Ethicon, a division of Johnson & Johnson.

"Dr. Levy brings a tremendous amount of experience successfully commercializing life-saving medical technologies," stated Guy DiPierro, founder and president of Chrono Therapeutics. "His passion, business acumen and leadership will be a huge asset to us."

Chrono Therapeutics (CHRONO) was founded in 2004 with a vision of transforming disease and addiction management in wearable, patient-optimized drug delivery. With real-time wireless connectivity and tailored behavioral support, Chrono's science of specifically tailoring the timing and dose sizes of drugs preempts predictable peak disease and addiction symptoms with an easy-to-use device. In partnership with the University of Basel, Switzerland, and three affiliate Universities, CHRONO has built a pipeline of pharmaceutical applications. The fruition of these efforts will see a widespread impact to better manage common conditions and diseases with next-generation "smart" drug products.

Sonrgy Secures Exclusive License from UC San Diego to Commercialize Drug Delivery Nanotechnology

Business Wire: February 5, 2014 – SAN DIEGO, CA, U.S.A. – Sonrgy, Inc., a biotechnology company developing focused drug delivery technologies, has announced that it has entered into an exclusive license agreement with the University of California for the company's core technology, an ultrasound-sensitive drug delivery platform.

The agreement grants the company the sole rights to develop and market the technology worldwide. Protecting the fundamental enabling technology establishes a significant barrier to potential competitors and is a vital step toward bringing the platform to the clinic.

Based on research conducted in the lab of Prof. Sadik Esener at the UC San Diego Moores Cancer Center, "the SonRx technology addresses longstanding challenges related to stability and controlled release in nano-scale drug delivery," stated Dr. Michael Benchimol, Sonrgy's chief technology officer. "We are excited to initiate the next steps of its commercial development."

Sonrgy is a preclinical stage biotechnology company based in San Diego, California, that is developing a targeted chemotherapy delivery platform to improve survival and quality of life for millions of cancer patients. Sonrgy's tiny nanocarriers safely transport potent chemotherapy drugs to cancer tumors and release high doses on command in response to a focused beam of

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ultrasound. These carriers deposit drugs directly at the tumor cell sites, avoiding the many serious side effects of toxic chemotherapy circulating in the blood stream. Nanocarriers can deliver chemotherapy before surgery to reduce tumor size, after surgery to prevent recurrence, and in situations when surgery is not possible to arrest tumor growth. This distinctive approach to delivering chemotherapy can be applied to many cancer tumors and enables more intensive treatment of the cancer, potentially improving effectiveness while reducing harmful effects on the rest of the body.

Envisia Therapeutics to Present at Glaucoma 360 Conference

Business Wire: February 4, 2014 – RESEARCH TRIANGLE PARK, NC, U.S.A. – Envisia Therapeutics today announced that it will present initial findings from its ENV515 program at the Glaucoma 360 New Horizons Forum on Friday, February 7, 2014, at the Palace Hotel in San Francisco. The presentation marks the company's first data presentation since its foundation last November. The conference, presented by Glaucoma Research Foundation (GRF), provides a forum for unique exchange on research innovation and advances in glaucoma treatment. Globally, glaucoma is a leading cause of preventable blindness.

"We are excited to share for the first time data supporting our lead pipeline product, ENV515, as well as insights into the transformational technology we are using for the development of innovative ocular therapies," said Ben Yerxa, Ph.D., chief scientific officer of Envisia.

ENV515 is an implantable, extended-release formulation of a marketed prostaglandin analogue that has the potential to offer glaucoma patients a therapeutic option that can sustain the reduction in intraocular pressure (IOP) over many months. Envisia uses the power of the proprietary PRINT® (Particle Replication In Non-Wetting Templates) technology to create particle-based ocular therapeutics that can deliver both small and large molecules in multiple formats.

Dr. Yerxa will present "Precisely Engineered Particles for Ocular Drug Delivery: ENV515 for Glaucoma and Beyond" as part of a moderated session titled "New Horizons in Glaucoma Drug Delivery," which begins at 9:30 a.m.

Envisia Therapeutics, formed by Liquidia Technologies in 2013, is a privately held biotechnology company focused on the development of novel ocular therapies. Envisia is leveraging the unique and powerful properties of the PRINT® technology to develop therapies for a variety of ocular conditions, beginning with ENV515 for glaucoma. ENV515 is a novel, implantable extended-release formulation of a marketed prostaglandin analogue with the potential to significantly limit disease progression and vision loss through improved product performance and patient compliance. Envisia is located in Research Triangle Park, North Carolina. For more information, please go to www.envisiatherapeutics.com.

Forest Laboratories, Inc., Completes $2.9B Acquisition of Aptalis

Business Wire: February 3, 2014 – NEW YORK, NY, U.S.A. – Forest Laboratories, Inc. (NYSE: FRX), a leading, fully integrated, specialty pharmaceutical company, today announced the completion of its acquisition of Aptalis, a privately held specialty pharmaceutical company focused on gastrointestinal disorders and cystic fibrosis. The companies will begin combined operations today, with Aptalis operating as a subsidiary of Forest Laboratories, Inc.

The acquisition of Aptalis strengthens Forest's gastrointestinal franchise in the United States and Canada, complements its growing cystic fibrosis business in Europe, and creates a cystic fibrosis business in the U.S. market. Forest expects the acquisition to add approximately $700 million in revenue and about $0.78 per share to the company's non-GAAP EPS in FY2015. The acquisition also adds assets to Forest's pipeline in both therapeutic areas. Postacquisition integration activities will begin today. As previously announced, Forest anticipates $125 million in cost synergies by fiscal year 2016.

"With the completion of the acquisition, Forest is well positioned to continue driving sales growth while realizing cost savings. The acquisition also fits our strategy of building blockbuster line calls to achieve economies of scale and make us more relevant to our customers," said Brent Saunders, chief executive officer and president of Forest. "Today marks a new opportunity to draw on the strengths and talents of both companies and emerge as a stronger Forest that is well equipped to deliver on its promise of bringing meaningful medicines to patients in our key therapeutic areas."

January

Clearside Biomedical, Inc., Announces Third Patent Allowance in the United States

Business Wire: January 29, 2014 – ALPHARETTA, GA, U.S.A. – Clearside Biomedical, Inc., announces the U.S. Patent and Trademark Office (USPTO) granted U.S. patent application no. 13/453,407 as U.S. patent no. 8,636,713 in a patent titled "Methods and Devices for Drug Delivery to Ocular Tissue Using Microneedle." This is the third patent allowance in the United States related to its proprietary microneedle drug delivery methods and devices.

U.S. patent no. 8,636,713 provides exclusivity through May 2, 2027, and covers in part a method of administering an anti-inflammatory drug to an eye of a patient by inserting a hollow microneedle into the patient's eye and infusing the drug into the suprachoroidal space of the patient's eye. The patent, exclusively licensed to Clearside, is the third generated from Clearside's alliance with the Georgia Tech Research Corporation and Emory University.

In April 2011 and June 2012, the USPTO issued method and device patents covering the company's drug delivery methods and devices for carrying out the methods.

Clearside Biomedical, Inc., headquartered in Alpharetta, Georgia, is a clinical-stage ophthalmic pharmaceutical company that develops and commercializes targeted therapeutics to treat sight-threatening diseases. Clearside treats the pathological changes to the blood retinal barrier that lead to retinal blindness by delivering therapeutics to the choroid and retina using a proprietary microinjection dosage form. Clearside Biomedical was founded by an executive team with extensive development and revenue growth expertise. This team strives for better delivery and performance of its therapeutic agents to improve the standard of care for patients with choroidal and retinal disease. Visit www.clearsidebio.com for more information.

Starpharma Commences Dendrimer-Docetaxel Clinical Trial

Business Wire: January 22 – MELBOURNE, Australia – Starpharma (ASX: SPL) (OTCQX: SPHRY) today announced that it has received the necessary approvals to commence a phase 1 human clinical trial for its dendrimer-enhanced docetaxel (Taxotere®) chemotherapeutic product, referred to as DEP™-docetaxel.

The trial will be conducted exclusively in Australia, at Nucleus Network's clinical facility at the AMREP/Alfred Hospital initially, with the plan to add 1 to 2 additional sites in the near future. The study will enroll approximately thirty patients with solid tumours. The primary objective of the study is to establish the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of DEP™-docetaxel, a new formulation of the major chemotherapeutic agent docetaxel, which is marketed worldwide under the trade name Taxotere®. The study will also include a preliminary assessment of the anticancer efficacy of DEP™-docetaxel.

Earlier preclinical studies of Starpharma's DEP™-docetaxel demonstrated the significantly superior anticancer effectiveness of the product compared with Taxotere® across a range of important cancer types including breast, prostate, lung, and ovarian cancer. In addition, DEP™-docetaxel exhibited a lack of the severe toxicity, neutropenia, which is the most important dose-limiting side effect of Taxotere®. Use of Starpharma's DEP™ technology also improved the water solubility and tissue targeting of docetaxel. This improvement means that unlike other marketed formulations of docetaxel, Starpharma's DEP™-docetaxel is detergent (polysorbate 80) free, delivering a number of potential patient tolerability and safety advantages compared with other formulations.

Starpharma chief executive, Dr. Jackie Fairley, said: "The commencement of this clinical trial of DEP™-docetaxel represents a key development milestone for this product and follows very strong preclinical results, which have included both improved efficacy and the reduction in important dose limiting side effects."

"The multiple, clinically significant benefits of Starpharma's DEP™-docetaxel will place the product in a very compelling competitive position. In addition, findings from this trial have potential flow-on benefit for Starpharma's dendrimer platform more broadly, particularly in oncology," said Dr. Fairley.

DEP™-docetaxel is the first clinical candidate using Starpharma's dendrimer-based DEP™ technology. The features of these products allow them to access a streamlined development pathway compared with a completely novel product.

The primary objective of the clinical study is to establish the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of DEP™-docetaxel given intravenously (IV), once every three weeks. The secondary objective is to identify the safety, pharmacokinetic, and tolerability profile of DEP™-docetaxel in patients with advanced cancer. Key outcomes of the study will be to define a recommended dose for future studies as well as to explore preliminary antitumour efficacy of the product.

Importantly, the study will also allow investigation of the impact of the improved dendrimer formulation on problematic side effects seen with Taxotere®, such as neutropenia (which was markedly reduced with the dendrimer formulation in preclinical studies), anaphylaxis, and hair loss. The study will also employ a variety of imaging techniques and specific investigations aimed at exploring antitumour efficacy. These include CT scans and bone scans, as well as tumour markers.

Consultant oncologist Dr. Jason Lickliter, MBBS, Ph.D., FRACP, director, Phase 1 Cancer Trials Program, Southern Health and Monash Institute of Medical Research, and medical director, Nucleus Network, has been appointed as the study principal investigator.

Starpharma's dendrimer-based drug delivery DEP™ technology has been utilised to reformulate and improve a number of marketed cancer drugs including docetaxel (Taxotere®), oxaliplatin (Eloxatin®), and doxorubicin. Preclinical studies of the dendrimer-enhanced versions have shown these reformulated DEP™ versions of the drugs to be superior to the commercially available formulation, often in multiple ways including improved efficacy, reduced toxicity, and lower side effects. Starpharma also has several partnered programs with leading pharma companies, including in oncology. For further information, please refer to the Starpharma website.

Alitair Announces Issuance of an Additional Patent Covering Its Platform Drug Delivery Technology, REA™

Business Wire: January 21, 2014 – MORRISTOWN, NJ, U.S.A. – Alitair Pharmaceuticals, Inc., a revenue-stage pharmaceutical company with multiple respiratory product candidates in development, today announced the issuance of U.S. patent no. 8,617,602 from the U.S. Patent and Trademark Office (USPTO) for its ion-exchange resin drug delivery technology, REA™.

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"Our proprietary ion-exchange resin drug delivery platform can be utilized across a range of therapeutic classes and with many different molecules," stated Alitair president and CEO William W. Howard, Ph.D. "The REA™ platform technology allows us to improve upon currently available therapies and create new solid-oral formulations with less frequent dosing schedules, both of which have been shown to improve patient adherence."

"Being awarded this third patent is an important milestone in our product development strategy and the growth of Alitair," continued Howard. "We will likely use this technology to provide protection for our orphan drug candidates, both of which can be formulated with our REA™ technology. This would extend the lifespan of our orphan candidates from 7 years to 20, further enhancing their value. We are also actively seeking funding and development partners to build on the momentum we've created and advance our product development programs."

Alitair Pharmaceuticals, Inc., develops medicines for the treatment of respiratory illnesses. Alitair has out-licensed two prescription cough candidates that use its proprietary ion-exchange resin technology (REA™). The company has two orphan drug candidates under development. Additional information about Alitair is available on the Alitair website at www.alitair.com.

Teva Expands CNS Specialty Business with Acquisition of NuPathe

Business Wire: January 21, 2014 – JERUSALEM, Israel – Teva Pharmaceutical Industries Ltd. (NYSE: TEVA) today announced that it has entered into a definitive agreement under which Teva will acquire NuPathe Inc. (Nasdaq: PATH) for $3.65 per share in cash, or approximately $144 million. In addition to the upfront cash payment, NuPathe shareholders will receive rights to receive additional cash payments of up to $3.15 per share if specified net sales of NuPathe's migraine treatment, ZECUITY®, are achieved over time.

ZECUITY is the first and only prescription migraine patch approved by the FDA for the acute treatment of migraine with or without aura in adults. ZECUITY is a disposable, single-use, iontophoretic transdermal patch that actively delivers sumatriptan, the most widely prescribed migraine medication, through the skin. ZECUITY provides relief of both migraine headache pain and migraine-related nausea. ZECUITY was approved based upon an extensive development program with phase 3 trials that included 793 patients using nearly 10,000 ZECUITY patches. In these trials, ZECUITY demonstrated a favorable safety profile and was effective at relieving migraine headache pain and migraine-related nausea two hours after patch activation.

With the addition of NuPathe's ZECUITY, Teva is expanding its portfolio of medicines that treat conditions affecting the central nervous system (CNS). Teva will now have access to NuPathe's proprietary technology including its transdermal delivery system for patients.

"We believe that ZECUITY is a great fit within our existing U.S. CNS business unit, with near-term sales and significant commercial potential," stated Mike Derkacz, vice president and general manager, Teva CNS. "ZECUITY enables rapid transdermal delivery of sumatriptan and bypasses the GI tract to avoid issues with oral intake, addressing an important, unmet patient need, especially for those with migraine-related nausea. At Teva, we will leverage our unique Shared Solutions infrastructure to support patient utilization of this important new medicine for migraine sufferers."

Following the successful completion of the tender offer, Teva will acquire all remaining shares not tendered in the tender offer through a second-step merger at the same price and with the obligation to make the same contingent cash consideration payments as to stockholders tendering their shares in the tender offer. The tender offer and withdrawal rights are expected to expire at 12:00 midnight, New York City time, on the 20th business day after the launch of the tender offer, unless extended in accordance with the merger agreement and the applicable rules and regulations of the Securities and Exchange Commission.

Elixir Medical Announces First Commercial Implant of the DESolve® Novolimus Eluting Coronary Scaffold System in Europe

Business Wire: January 15, 2014 – SUNNYVALE, CA, U.S.A. – Marking a milestone in the evolution of fully bioresorbable drug-eluting scaffolds for interventional cardiology, the first commercial implant of Elixir Medical's CE Mark-approved DESolve Novolimus eluting coronary scaffold was performed in Germany by Prof. Dr. Holger Nef, head of the Cardiac Catheterization Laboratory, University Hospital Giessen, Giessen, Germany.

Elixir's fully bioresorbable DESolve scaffold for coronary artery disease restores blood flow to the heart like metallic stents but then dissolves to leave behind a treated artery that can function and move more naturally because it is free of a permanent implant. Developed from a proprietary and proven poly(L-lactide)-based polymer, DESolve provides optimal strength and support to the artery while delivering the novel antiproliferative drug Novolimus.

The unique advantages of the DESolve scaffold system include (a) maintaining radial strength and vessel support for the necessary period of vessel healing while degrading in one year; (b) increasing lumen area within six months; (c) self-apposing to the vessel wall up to the nominal deployed diameter; and (d) providing a wide margin of expansion.

"The fully bioresorbable DESolve system is easy to deliver. The acute performance of the scaffold demonstrated excellent stent apposition to the vessel wall and low recoil, and the patient is doing well," said Prof. Nef. Director of cardiology at University Hospital Giessen Prof. Dr. Christian Hamm further commented,

"I am confident that Elixir's scaffold system will drive forward the field of vascular intervention."

Developing an optimal bioresorbable scaffold had long been a challenge in the coronary vascular industry because it requires a level of strength and support that previously only permanent metallic stents had been able to provide while degrading in a timely manner and maintaining excellent clinical outcomes. The DESolve Novolimus eluting bioresorbable coronary scaffold overcomes these challenges and achieves vascular restoration within six months. Elixir's DESolve accomplishes this objective years sooner than competitive scaffolds.

"Elixir's DESolve has excellent clinical trial data to support its use. It is the first scaffold to degrade in one year, demonstrate lumen area increase within six months, and maintain the lumen area beyond one year," said Stefan Verheye, M.D., Ph.D., ZNA Middleheim Hospital, Antwerp, Belgium, and coprincipal investigator of the DESolve Nx trial. "These key differentiating features will create a paradigm shift in the treatment of patients with cardiovascular disease."

The DESolve Nx pivotal trial enrolled 126 patients at 13 centers in Europe, Brazil, and New Zealand. Excellent one-year safety and efficacy results for the DESolve Novolimus eluting coronary scaffold system had been announced at the Transcatheter Therapeutics 2013 scientific conference in San Francisco in October 2013.

At one year, the DESolve Nx trial demonstrated a low MACE (major adverse cardiac events) rate of 5.69% with no definite scaffold thrombosis. Results using MSCT (multi-slice coherence tomography), a noninvasive imaging modality to visualize coronary arteries and the manifestations of coronary artery disease, demonstrated that the lumen area measurements of treated vessels at one year were maintained to the results that were observed at 6 months using other imaging modalities.

"Elixir is proud to fulfill its commitment of providing the broadest and most innovative product portfolio for cardiologists to address their patients' needs," said Motasim Sirhan, president and chief executive officer of Elixir Medical. "The fully bioresorbable DESolve scaffold system holds the promise of transforming the interventional cardiology industry by raising the bar in clinical outcomes and leaving no permanent implant behind."

The fully bioresorbable DESolve Novolimus eluting scaffold system roll out will begin at initial centers in Europe. The scaffold is currently available in diameters of 3.0, 3.25, and 3.5 mm and lengths of 14, 18, and 28 mm. Additional sizes will be available in 2014.

Elixir Medical is the only company with three CE Mark-approved drug-eluting systems spanning all market segments: the DESolve Novolimus eluting bioresorbable coronary scaffold system, the DESyne® BD Novolimus eluting coronary stent system (with biodegradable polymer), and the DESyne® Novolimus eluting coronary stent system (with durable polymer). The company has also received U.S. Food and Drug Administration IDE (Investigational Device Exemption) approval to commence the EXCELLA III clinical trial in the United States with Elixir's durable polymer Novolimus eluting coronary stent system.

RBCC Partner Therakine Presents Novel Drug Delivery Technology at Biotech Showcase

Business Wire: January 15, 2014 – MIRAMAR BEACH, FL, U.S.A. – Rainbow Coral Corp. (OTCBB: RBCC) joint venture partner Therakine, Ltd., presented its new novel drug-delivery technology at one of the world's largest and most important gatherings of life sciences investors this week at the Biotech Showcase in San Francisco.

RBCC is partnering with Therakine to market and develop a revolutionary new injectable sustained-release technology poised to vastly improve patients' use of a crucial drug in the fight against drug and alcohol dependence. The joint venture plans to soon offer the only intramuscular programmable release of the powerful opioid receptor antagonist naltrexone available anywhere in the $142.5 billion drug delivery industry.

"We're extremely thrilled with the response we've received from attendees," said RBCC CEO Kimberly Palmer. "We're already discussing the development of new drug delivery programs using this same innovative protocol produced by Therakine. I expect to begin talks soon with more potential partners that are well positioned to capitalize on this technological breakthrough. "The future of this protocol is extraordinarily promising, and it has a lot of people excited," she continued. Phase II of development on the drug-delivery tech is currently underway, focusing on micronization of the technology as well as extension of its sustained release time.

RBCC's biotech division, Rainbow BioSciences, is working with partners such as Therakine to capitalize on the incredible growth of the global drug delivery market by delivering new medical and research technology innovations in order to compete alongside companies such as Bristol Myers Squibb Co. (NYSE: BMY), Biogen Idec Inc. (NASDAQ: BIIB), Abbott Laboratories (NYSE: ABT), and Valeant Pharmaceuticals International (NYSE: VRX). For more information on RBCC's other biotech initiatives, please visit www.rainbowbiosciences.com/investors.html.

ARIAD and Medinol Announce Initiation of Two Registration Trials of the NIRsupreme™ Ridaforolimus-Eluting Stent for Use in Coronary Artery Disease

Business Wire: January 14, 2014 – CAMBRIDGE, MA, U.S.A., and TEL AVIV, Israel – ARIAD Pharmaceuticals, Inc. (NASDAQ: ARIA) and Medinol, Ltd., today announced the initiation of two registration trials of Medinol's NIRsupreme™

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ridaforolimus-eluting coronary stent system incorporating ARIAD's mTOR inhibitor, ridaforolimus. The two NIRsupreme clinical trials are randomized, single-blind, global studies taking place in the United States, Europe, Israel, and Canada and will enroll approximately 2,200 patients with coronary artery disease. ARIAD licensed ridaforolimus to Medinol for use in drug-eluting stents in 2005. Drug-eluting stents (DES) are now implanted in over 500,000 patients yearly in the United States.

The commencement of patient enrollment in Medinol's clinical trials, along with the submission of an investigational device exemption with the U.S. Food and Drug Administration, triggers milestone payments to ARIAD of $3.75 million, with the potential for additional regulatory, clinical, and sales milestones, as well as royalties on product sales.

The BIONICS trial aims to show that the NIRsupreme stent is comparable (non-inferior) to a comparator drug-eluting stent with the primary endpoint of coronary target lesion failure (a composite of cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization) at 12 months. This trial is expected to enroll approximately 1,900 patients.

The NIREUS trial aims to demonstrate angiographic non-inferiority of the NIRsupreme stent to a comparator stent and has a primary endpoint of late loss in lumen diameter within the stent determined by coronary angiography at six months. This trial is expected to enroll approximately 300 patients.

"We are pleased to have one of the most innovative and successful medical device companies advance the development and potential commercialization of drug-delivery stents incorporating ridaforolimus," said Timothy P. Clackson, Ph.D., president of research and development and chief scientific officer at ARIAD. "We believe that Medinol has developed a unique elastomeric formulation and stent platform, and we are delighted by the value created through this successful long-term collaboration with a true innovator."

ARIAD entered into a nonexclusive agreement with Medinol to develop and commercialize stents and other medical devices to deliver ridaforolimus to prevent reblockage of injured vessels following stent-assisted angioplasty. ARIAD is eligible to receive additional regulatory, clinical, and commercial milestones of up to $34.75 million, if two products are developed, plus royalties on worldwide product sales. ARIAD is responsible for supplying ridaforolimus to Medinol, and Medinol is responsible for the development and commercialization of the medical devices delivering ridaforolimus. These rights are separate from those licensed to Merck for use of ridaforolimus in oncology.

"We are proud and excited to initiate the BIONICS and NIREUS clinical trials," said Yoram Richter, Ph.D., chief scientific officer at Medinol. "NIRsupreme, the first ever elastomer-based DES, is the outcome of meticulous research towards uniform, controlled drug release. We believe that this is the evolution that interventional cardiologists have been waiting for. Medinol is privileged to cooperate with ARIAD, a leading drug developer, and has high expectations for this partnership," Dr. Richter concluded.

Fabrus Obtains Chimerasome Nanoparticle Technology

PRNewswire: January 13, 2014 – SAN DIEGO, CA, U.S.A. – Fabrus, Inc., a San Diego based antibody discovery company, announced today that it has obtained worldwide exclusive rights to Chimerasome™ nanocage technology originally developed by Chimeros, Inc. The foundation of Chimerasome technology is a single protein that can be manipulated to form a spherical protein shell, which can encapsulate drugs and be coupled to antibodies externally, allowing very specific cellular targeting of the drug payload.

Miguel de los Rios, Ph.D., Fabrus's vice president of R&D and the inventor of the Chimerasome and founder of Chimeros, Inc., commented, "Chimerasome technology can allow the delivery of thousands of active drug molecules per antibody to a target, compared to perhaps a half a dozen molecules using traditional antibody drug conjugate or ADC technology. In addition, we can adjust the protein building blocks to allow the opening of the nanocage based on environmental cues. This can allow even more precise drug delivery than traditional ADC technologies."

"The Chimerasome technology will allow us to create unique drug particles by combining antibodies developed on the Fabrus platform with the Chimerasome nanocage," stated Vaughn Smider, M.D., Ph.D., founder of Fabrus. "The technology could enable us to deliver massive payloads of either small molecule drugs or unique biologics like siRNA to very targeted locations in the body, broadening the therapeutic utility of our antibodies."

Fabrus is the first company to bring the speed and flexibility of small molecule screening to the field of fully human antibody therapeutics, while being unencumbered by existing antibody engineering intellectual property. The novel discovery format is analogous to a combinatorial chemistry library and enables direct cell-based screening, opening novel targets to antibody therapeutics such as G-protein coupled receptors or ion channels. Fabrus investors include OPKO Health and Pfizer, Inc. For more information, go to www.fabrus.net.

A.P. Pharma Announces Appointment of New Directors and Effective Date of Name Change and Reverse Stock Split

Business Wire: January 13, 2014 – REDWOOD CITY, CA, U.S.A. – A.P. Pharma, Inc. (OTCBB: APPA), a specialty pharmaceutical company, today announced that it has changed its name to Heron Therapeutics, Inc., and effected a 1-for-20 reverse stock split, both effective January 13, 2014. The reverse split is being implemented to increase the company's stock price in support of the company's pending application to list on the NASDAQ Capital Market. Assuming satisfaction of listing standards, the company expects to list on NASDAQ by the end of January.

The company is also expanding its board of directors and today announced the appointment of three new independent directors. Joining the Heron Therapeutics board of directors effective today are John Poyhonen, president and chief executive officer of Senomyx, Inc., Kimberly Manhard, senior vice president of regulatory affairs and development operations at Ardea Biosciences, a subsidiary of AstraZeneca PLC, and Craig Johnson, a senior advisor and consultant in the biopharma industry.

"As we pursue a new vision for Heron Therapeutics, we are excited to be adding to our board seasoned executives with the wealth of experience that John, Kimberly, and Craig bring," said Barry D. Quart, Pharm.D., chief executive officer of Heron Therapeutics. He continued: "2014 promises to be a landmark year for Heron. As we advance our lead drug candidate, Sustol, toward a planned commercial launch, advance our postoperative pain program to clinical studies, and further exploit our polymer-based platform, the combined operations, strategic, and financial expertise of these veterans will be invaluable."

Mr. Poyhonen, MBA, will serve as chair of Heron's compensation committee of the board of directors and as a member of the audit committee. He has provided senior level experience and served on the board of companies in the biopharma industry for more than 15 years. He joined Senomyx, Inc., in October 2003 and served in various executive positions prior to his current role as president and CEO. Prior to Senomyx, he was vice president of national sales at Agouron Pharmaceuticals, a Pfizer, Inc., company, where he played a key role in the successful commercial launch of Viracept®, a protease inhibitor for the treatment of HIV.

Ms. Manhard will serve on Heron's compensation committee, audit committee, and nominating and governance committee. In addition to her role as senior vice president of regulatory affairs and development operations at Ardea Biosciences, she also serves as Ardea's corporate compliance officer. Prior to joining Ardea, Ms. Manhard served in various senior roles at successful biotechnology and pharmaceutical companies, including roles as vice president of regulatory affairs at Exelixis, Inc., at Agouron, where she was responsible for the international registration of Viracept, and at Bristol-Myers Squibb, where she was responsible for international registration of Taxol.

Mr. Johnson will chair Heron's audit committee and serve as a member of the nominating and governance committee. He has served in senior executive and advisory roles and on the boards of directors of biotechnology companies for over 20 years. He is currently a director for Mirati Therapeutics, Inc., Adamis Pharmaceuticals Corporation, and La Jolla Pharmaceutical Company. Previously, he served as chief financial officer at Torrey Pines Therapeutics prior to its acquisition by Raptor Pharmaceutical Corp. and at MitoKor, Inc., prior to its acquisition by Micrologix Biotech Inc. Earlier in his career, he practiced as a CPA with Price Waterhouse.

The company's trading symbol will be "APPAD" for up to 20 trading days after the split to designate that it is trading on a post-reverse split basis. Upon listing on NASDAQ, the trading symbol will change to "HRTX." ■

Controlled Release Society
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Calendar of Events

2014

International Microneedles Conference
May 19–21
Baltimore, MD, U.S.A.
www.international-microneedles.org/about.html

IWPCPS-16
June 16–19
Prague, Czech Republic
www.assainternational.com/workshops/iwpcps-16

41st Annual Meeting & Exposition of the Controlled Release Society
July 13–16
Chicago, IL, U.S.A.
controlledreleasesociety.org

17th International Pharmaceutical Technology Symposium
September 8–10
Antalya, Turkey
www.ipts-hacettepe.org

Third Symposium on Innovative Polymers for Controlled Delivery
September 16–19
Suzhou, China
www.sipcd.cn

5th Course on the BBB in Drug Development
October 1–3
Uppsala, Sweden
www.uc.pt/fmuc/gai/cursosavancados/BBB