CRS Leading Delivery Science and Technology

Newsletter

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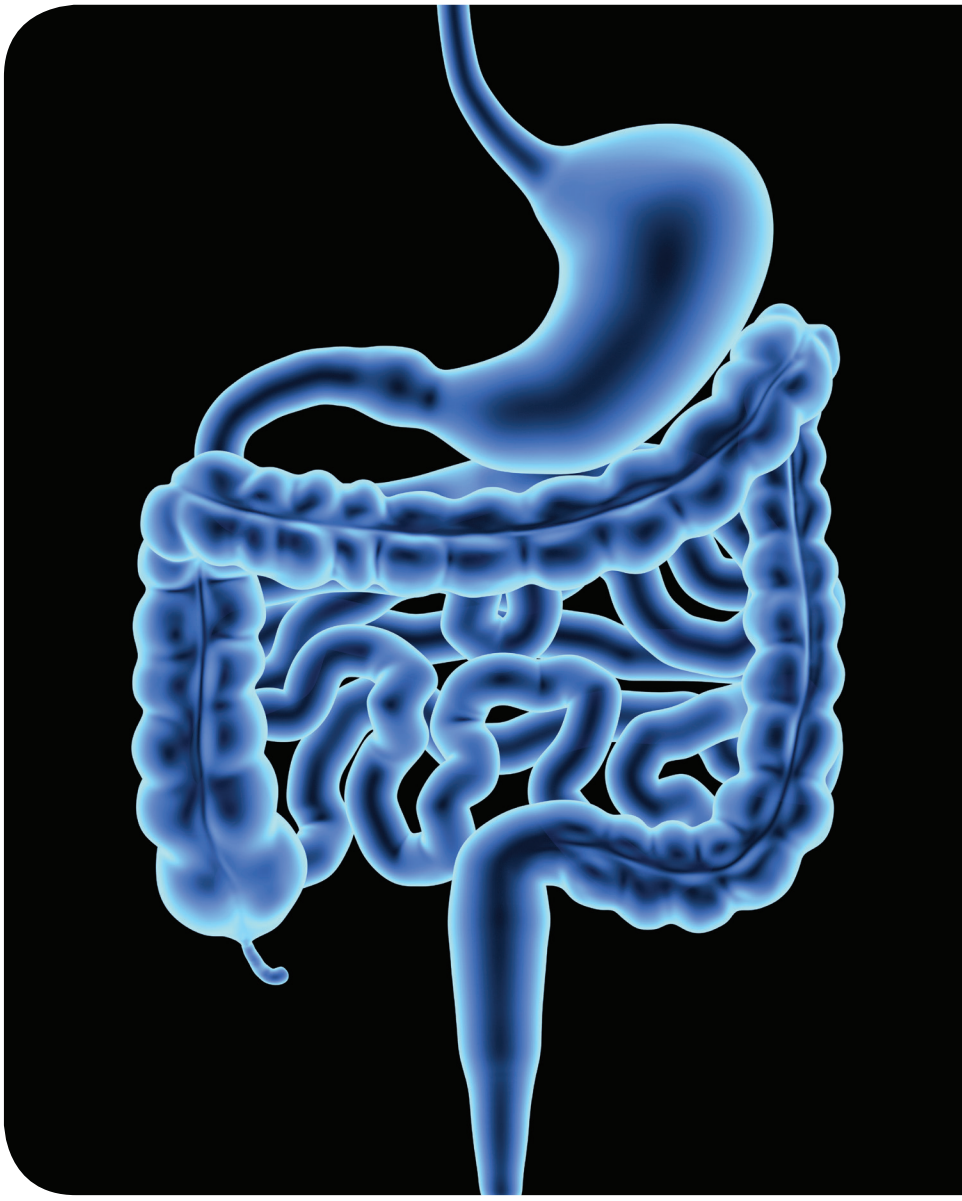


What's Inside

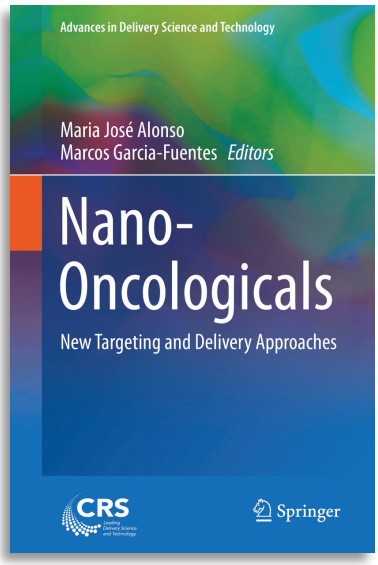
CRS Advances in Delivery Science and Technology Book Series

CRS Leading Delivery Science and Technology

NEW TITLE

Nano-Oncologicals

New Targeting and Delivery Approaches



Edited by Maria José Alonso, Professor of Biopharmaceutics and Pharmaceutical Technology at the University of Santiago de Compostela (USC), Spain; Marcos Garcia-Fuentes, Associate Professor of Pharmacy at USC, Spain

- Establishes a comprehensive background to any scientist entering the field of cancer nanomedicine
- Revises novel anticancer strategies including targeted therapies, immunomodulation, and emerging therapeutic technologies
- Focuses several chapters on translational aspects for nano-oncologicals, reviewing first-hand experiences from companies working on this area

The volume begins with an introduction describing the biological barriers associated with cancer therapy and highlighting ways to overcome such barriers through the use of nanotechnology. This is followed by an analysis of the two major targeting strategies currently under investigation in cancer therapy: namely, the targeting of cancer cells and the targeting of the immune system. Beyond these targeting options, this book presents the most recent technological advances in the area of nucleic acid-based therapies, along with those in the area of theranostics, where the design of multifunctional nanocarriers becomes vital. The book concludes with an overview of regulatory and toxicological issues, which are critical in their translational pathway, and the presentation of a nucleic acid-based therapy case study.

2014, XIV, hardcover, 473 pages.

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

controlledreleasesociety.org

#8754REV-11/2014

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CRS Newsletter

Leading Delivery Science and Technology

Vol. 31 • No. 6 • 2014

Table of Contents

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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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Roderick B. Walker
Rhodes University
South Africa

Salamanders, Zebrafish, and CRS

This issue of the *CRS Newsletter* contains a fascinating summary of five published articles that have some focus on animals as a source of compounds with the potential to treat human conditions or as models to facilitate understanding of disease and biological functions. Of particular interest are the potential wound-healing peptide sources from salamander skin and the zebrafish model used to understand cyanide poisoning. Two interesting Scientifically Speaking articles appear as well: using immobilised lipase to improve evaluation of lipid-based formulations, and evaluating the permeability, stability, and toxicity of a novel peptide.

The interview with Prof. Mitragotri—a prominent leader in the field of drug delivery and biomaterials including transdermal delivery of proteins and peptides and the development of models to predict transport across the skin and mucosal barriers—makes for interesting reading. In a similar vein, the "Volunteer Spotlight" features interviews with David Chen and Medha Joshi, who have different degrees of experience as CRS volunteers, in which they share their motivation for and highlight their expectations of their involvement with the organization.

The active and award-winning UKICRS chapter provides a report on three sessions related to cell responses at surfaces, design and development of regenerative medicines, and the industrial application of biomaterials that the chapter facilitated at the UK PharmSci meeting held in September.

You will no doubt be aware that CRS is gearing up for the annual meeting to be held in Edinburgh, Scotland, a meeting that promises to be as innovative in its delivery as the science of delivery that we, as scientists, present when we attend the meeting. The call for abstracts is out, so get onto submitting as soon as you are able. In addition, you as members have been asked to consider nominating colleagues for awards and positions within CRS. Also, be on the lookout for calls for volunteers for various committees.

Finally, I would like for all of us to take a few moments to reflect on the Ebola epidemic and other diseases that have affected some of the poorest people in the world this year. There are opportunities to learn from these and other events so that innovative and out-of-the-box thinking can find the treatments and cures to overcome many of these conditions.

As the year draws to a close, I wish you all a happy and blessed time with family and friends. I suggest you take a break at the end of what has been an extremely busy and I am sure productive year, and I wish that 2015 will be a peaceful and prosperous year for all. ■

Art Tipton
Southern Research Institute
Birmingham, Alabama, U.S.A.

Products!

I jotted notes for this update as I flew back from the Partnership Opportunities for Drug Delivery (PODD) conference in Boston. CRS was well represented at this conference. The conference, now in its fourth year, was again chaired by Board of Scientific Advisors (BSA) member Barbara Lueckel. Participating in talks or panel discussions were Board members Andy Lewis and James Oxley, BSA member Richard Korsmeyer, and active CRS member Julia Rashba-Step. Elsewhere at the conference were many other CRS members. I got to participate in a "fireside chat" with Bob Langer that kicked off the conference; as part of that we included quotes from many people who worked with (and in most cases were mentored by) Bob, including Annual Meeting Program Committee (AMPC) chair Justin Hanes, head of the BSA Edith Mathiowitz, and former AMPC chair and current Annual Meeting Committee member Mark Prausnitz. Indeed, it is hard to imagine a group of people gathered anywhere to discuss delivery science that does not include a significant contingency of people connected to CRS.

I titled this document "Products!" partly because of the PODD conference and partly based on thoughts I have had over the last several months. Similar to all CRS members, I love science. But we all know the way to really impact the world is to have that science lead to products. How well do we at CRS do at that?

One of the wonderful aspects of CRS is the diversity of our membership. When I think about products at CRS, I always first think about our Consumer and Diversified Products (C&DP) group. As our C&DP Division—whose focus includes encapsulation and controlled release research for food, nutraceuticals, personal care, cosmetics, home care, agriculture, textiles, and coatings—this group even has "products" in their name! As you go through the next year at CRS, if C&DP is not your focus, reach out to this group, or attend one of the C&DP-related sessions or meetings at the annual meeting in 2015. When I interact with them, I am always impressed with the strong fundamental science coupled with a focus on getting products developed. I often think the sense of urgency is a reflection of the diversity of this sector and the shorter development times (as compared to drugs). Those of us who have spent most of our careers in the drug sector have much to learn from our C&DP colleagues.

As PODD is primarily a business conference, Barbara gave an update on major drug delivery deals over the last 12 months: Sanofi and MannKind on inhaled insulin as a headline for other inhalation advances, some increased efforts in ocular such as the Allergan/InnoCore license, targeted delivery to overcome the blood brain barrier such as the MedImmune/biOasis partnership, or device combinations such as the Mallinckrodt/Medtronic intrathecal delivery or Novo Nordisk/Zosano on microneedle delivery. We are in the midst of a robust and exciting time in drug delivery science!

I use on oft-repeated point that the research teams perform the first 95% of getting a product to market and then the development people perform the next 95%. We are often guilty of underestimating the role of our colleagues. My suggestion: use CRS to learn more about the entire process of getting products to market. Attend an industry session or the Soapbox Sessions at the CRS Annual Meeting, visit with our exhibitors, or use our membership directory to identify a person who can help turn your R&D idea into a product. It is important not to too early fall in love with your idea and think that all platforms can be products. Use our members to find final users of your potential product, and talk to several dozen rather than to a small team close to your research. Remember that regulatory agencies around the world do not approve raw materials or platforms but final products, so get their input early and often as you advance a product.

I have had the experience, likely common to others, of developing a new delivery platform. It was a research interest, and I pursued it for more than a year developing many product "ideas." Later, with the formation of a cross-functional team focused on a single lead product, through advanced development, manufacturing, and clinical experience, the knowledge of the technology was accelerated much further than in the research phase.

I closed my last commentary looking forward to our annual meeting next year in Edinburgh with a Scottish joke. I will close this commentary with a quote from the famous Scottish author Sir Walter Scott, from his *Antiquary:* "It's no fish ye're buying—it's men's lives."

The relevance of this quote, used by a fisherman's wife when a buyer complained about the cost of fish, is to remind the buyer of the cost measured not in fish alone but in the hard work and danger her husband and sons experienced, even the risk of death, in catching those fish. So as we look to develop products, let us remember the cost and dedication, not measured in a single research or manufacturing step but the rich tapestry we all are fortunate to be part of in developing products. In Bob Langer's discussion at PODD, he talked about the "stubbornness gene." Let us renew our efforts to embrace that gene and to get more products to market, thereby not only benefiting those of us around the world interested in delivery science but the much larger population we all serve. ■

Biomaterial and Drug Delivery Focused Research with Samir Mitragotri at University of California, Santa Barbara

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

Samir Mitragotri is a prominent leader in the field of drug delivery and biomaterials. His contribution in the field of transdermal drug delivery was noticed by the community when his group successfully published the delivery of vaccines (proteins), insulin (peptides), and siRNA via skin into the blood stream using painless needle-free methods like sonophoresis (low frequency ultrasound) and liquid jet injector, which could have a potential impact in the field of HIV, hepatitis C, and hepatitis B. Another research area, which led to multiple insightful publications, is the development of mathematical models to describe and predict transport across the skin and mucosal barriers. Dr. Mitragotri has made significant contributions in the development of novel mucoadhesive polymer devices, biomaterials with carefully designed morphologies for targeted drug delivery, and cell-based nanoparticle delivery methods. His group is also active in creating biodegradable and biocompatible particles with the size, shape, and flexibility of red blood cells and synthetic platelets with applicability in the field of pathology and drug delivery.

His current research focuses on understanding fundamental processes in biological systems and development of new biomaterials and technologies for diagnosis and treatment of various pathological conditions including diabetes, cardiovascular disease, and infectious disease. With the intent of bringing the academic research to commercial application, Dr. Mitragotri has cofounded seven companies: Sontra, fqubed, Stratagent, Seventh Sense, Dx, Entegra, and Convoy.

Dr. Mitragotri obtained his bachelor's degree in chemical engineering from the Institute of Chemical Technology (ICT) in Mumbai, India, in 1992 and his Ph.D. from Massachusetts Institute of Technology (MIT) in Cambridge, MA, U.S.A., in 1996. He has since been a faculty member in the Department of Chemical Engineering at the University of California, Santa Barbara (UCSB). He also served as the founding director of UCSB's Center for Bioengineering and director of translational medical research laboratories. He has published over 175 publications, given over 250 invited lectures, and is an inventor on 90 pending or issued patents. His work has been cited over 14,000 times and has been highlighted by various popular news media, including the *New York Times*, *USA Today*, and *Discover Magazine*. He has mentored over 50 graduate students and postdocs and over 100 undergraduate students.

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.

He has been awarded multiple national and international recognitions, including the CRS Young Scientist Award, American Institute of Chemical Engineers Allan P. Colburn Award for his outstanding publication record, and world's top young innovators award (TR35) by MIT's *Technology Review* magazine in 1999. He is an elected fellow of the National Academy of Inventors, American Association for the Advancement of Science, and American Institute for Medical and Biological Engineering. He currently serves as an associate editor of the *Journal of Controlled Release*.

Mitragotri received the 2008 CRS Young Investigator Award.

Q *What makes the red blood cells and blood platelets being developed in your laboratory potentially superior over other biomaterials being used for the same purpose? Have you already performed animal studies on these particles, and what are the results?*

A The unique feature is that the materials developed in our laboratory provide morphological mimicry of natural red blood cells and platelets. Many synthetic materials that are designed for intravascular drug delivery suffer from limited vascular circulation, low targeting, and the inability to negotiate biological barriers. To further complicate the matter, these requirements must be met *simultaneously* while also limiting toxic effects on the patient. Mother Nature has already provided us with many examples where these tasks are successfully performed. These examples include red blood cells and platelets. We have developed synthetic particles that provide morphological mimicry of these natural cells. Our research has shown that such morphological mimicry plays an important role in their biological function. This observation fits into the bigger question that we pose in our lab, that is, while it is known that specific interactions mediated by ligand-receptor association are ubiquitous in biology, does the physical form of ligand presentation defined by the size, shape, deformability, and so on impact the biological outcome? Our research indeed demonstrated

that physical parameters underlying ligand presentation do matter. Specifically, synthetic particles that mimic the shape and flexibility of natural platelets exhibit better binding to vascular injuries compared with their spherical and rigid counterparts. This finding forms the basis of our platelet-like nanoparticles. We have performed *in vivo* studies with our platelet-like nanoparticles, which showed excellent wound targeting and hemostasis. These studies have been recently published in *ACS Nano*.

Q *Please tell us about some of the exciting research projects being investigated in your lab.*

A Several exciting research projects are ongoing in our lab; I will mention two in the interest of space.

The first project deals with the treatment of bacterial biofilms that build up in tissues, especially skin. Biofilm-protected microbial infections in skin are a serious health risk that remains to be adequately addressed. The lack of progress in developing effective treatment strategies is largely due to the transport barriers posed by the stratum corneum of the skin and the biofilm itself. We have developed ionic liquids for simultaneous biofilm disruption and enhanced antibiotic delivery across the skin layers. This work establishes the use of ionic liquids for topical drug delivery and as a new arsenal of materials against antibiotic-resistant bacterial infections in skin.

The second project deals with targeted delivery of drugs and imaging agents to inflamed tissues, which are often found in cases of cancer, Alzheimer's disease, and arthritis. We use monocytes for this purpose, as they possess a unique ability to target and penetrate into sites of inflammation. We take advantage of the natural ability of monocytes to target inflammation and deliver flat polymeric particles ("cellular backpacks") that attach strongly to the surface of monocytes but do not undergo phagocytosis because of the cellular backpack's disk-like shape and flexibility. In two separate *in vivo* inflammation models, backpack-laden monocytes exhibited increased accumulation in inflamed tissues. Cellular backpacks, and their abilities to attach to monocytes without impairing monocyte functions and to "hitchhike" to a variety of inflamed tissues, offer a new platform for both cell-mediated therapies and targeting inflamed tissues.

Mitragotri served on the Annual Meeting Program Committee for the 2014 CRS Annual Meeting in Chicago.

Q *What are the top five research articles from your laboratory that have made the most impact?*

A It is a challenge to select a handful of papers because the impact can be measured in so many different ways. Some articles have made a deep impact on fundamental understanding, whereas others have led to a new technology. Nevertheless, here is a list of five representative papers:

Hsu, T, Mitragotri, S. Delivery of siRNA and other macromolecules into skin and cells using a peptide enhancer, Proc. Natl. Acad. Sci. U.S.A. 108: 15816-15821 (2011). This article reports a peptide identified by phage display named skin penetrating and cell entering (SPACE) peptide for transdermal delivery of siRNA and other macromolecules. siRNAs are potential therapeutics for various dermatological diseases including psoriasis, atopic dermatitis, and cancer. Their utility is, however, limited by their low absorption across the stratum corneum and into viable cells of skin. SPACE peptide offers a potential solution to this problem.

Doshi, N, Zahr, A, Bhaskar, S, Lahann, J, Mitragotri, S. Red blood cell-mimicking synthetic biomaterial particles, Proc. Natl. Acad. Sci. U.S.A. 106: 21495-21499 (2009). Inspired by the superior design properties of red blood cells, we synthesized particles that mimic the key structural and functional features of red blood cells. Similar to their natural counterparts, red blood cell–mimicking particles reported in this article possess the ability to carry oxygen and flow through capillaries smaller than their own diameter. Further, they can also encapsulate drugs and imaging agents. These particles provide a paradigm for the design of drug delivery and imaging carriers because they combine the functionality of natural red blood cells with the broad applicability and versatility of synthetic drug delivery particles.

Champion, JA, Mitragotri, S. Role of target geometry in phagocytosis, Proc. Natl. Acad. Sci. U.S.A. 103: 4930-4934 (2006). This manuscript reports a surprising finding that particle shape plays a dominant role in phagocytosis by macrophages. Specifically, the local shape determines the complexity of the actin structure that must be created to initiate phagocytosis and allow the membrane to move over the particle. Failure to create the required actin structure results in simple spreading and not internalization.

Arora, A, Hakim, I, Baxter, J, Rathnasingham, R, Srinivasan, R, Fletcher, DA, Mitragotri, S. Needle-free delivery of macromolecules across the skin by nanoliter-volume pulsed microjets, Proc. Natl. Acad. Sci. U.S.A. 104: 4255-4260 (2007). Despite their long history, needle-free liquid jet injectors are not commonly used as a result of

Interview with Mitragotri continued on page 6

Interview with Mitragotri continued from page 5

frequent pain and bruising. We hypothesized that pain and bruising originate from the deep penetration of the jets and can potentially be addressed by minimizing the penetration depth of jets into the skin. Using a new strategy of jet injection, pulsed microjets, we reported on the delivery of protein drugs into the skin without deep penetration. The high velocity (v > 100 m/s) of microjets allows their entry into the skin, whereas the small jet diameters (50–100 μm) and extremely small volumes (2–15 nanoliters) limit the penetration depth (approximately 200 μm).

Karande, P, Jain, A, Mitragotri, S. Discovery of transdermal penetration enhancers by high-throughput screening, Nat. Biotechnol. 22: 192-197 (2004). In this paper, we reported particular mixtures of penetration enhancers that increase skin permeability to macromolecules (approximately 1–10 kDa) by up to approximately 100-fold without inducing skin irritation. The discovery of these mixtures was enabled by an experimental tool, *in vitro* skin impedance guided high-throughput (INSIGHT) screening, which is >100-fold more efficient than current tools.

Q *You have been involved in commercial translation of several of your technologies. What are some of the major challenges faced during translation of research ideas into commercial products, and what did you learn in the process?*

A The journey of a technology from ideation to a commercially successful drug delivery system is long and difficult, as evidenced by a small number of FDA-approved products that utilize advanced drug delivery systems in spite of a strong early research pipeline. At each step of translation, there exist roadblocks that can slow down progress. In our efforts to translate our ideas into products, we have encountered our fair share of challenges and have learned several lessons.

The first lesson is to put the idea to a rigorous test in its early stages. Ideas that form the foundation of potential products need to be tested and verified as soon as possible. Proof of concept *in vivo* studies are essential in confirming that the concept is viable and can provide therapeutic benefits. Given the high rate of fallout during *in vitro* to *in vivo* translation, it is critical that the idea be put to the *in vivo* test as soon as possible.

Following up with strong publications and patents is also key. Strong publications provide validation of significant scientific breakthroughs through peer review. Patents, obviously, are an essential component of commercial development as well. Another lesson we learned from these experiences is to value simplicity. All things being equal, a simple solution is a winning solution. Simplicity is not often considered a key principle in academic research; hence, a critical evaluation of the technology from the perspective of simplicity must take place. Having the right group of individuals and collaborators around the technology is also the key. Converting academic technology into a product requires a team with diverse expertise working with the right mindset.

Q *What are future topics of interest in your laboratory research?*

A We are working on several new areas within drug delivery. One topic of particular interest is hybrid synthetic-biological methods for targeted drug delivery. Synthetic carriers provide several advantages including drug encapsulation and precise engineering, whereas biological systems, in particular circulatory cells such as red blood cells and monocytes, provide unique advantages including long circulation and deep tissue penetration. Hybrid systems that combine synthetic and biological systems offer advantages of both systems while avoiding their limitations. Another area of interest is ratiometric drug delivery systems. Combinations of drugs are more effective compared with single drugs for many diseases, especially cancer. However, delivery of drug combinations in controlled proportions is a significant challenge and requires systems that are able to independently incorporate and release multiple drugs.

Q *After finishing graduate school, what made you choose an academic career? How did your background from MIT and ICT affect that decision-making process? Which individuals have had an impact on you?*

A Ever since I can remember, I have found an academic career very appealing. I was fortunate to have phenomenal mentors throughout my education, especially at MIT and ICT. I idolized them and wanted to become like them. That's the primary reason for me choosing an academic career. I have been deeply influenced by my mentor Bob Langer. His approach to research, his way of thinking about problems, and his pursuit of solutions have been a source of inspiration. I have also been impacted by my students. They have brought their own views and approaches to our research group and have thus enriched my life. I am extremely proud of their accomplishments and success.

Q *Please share your hobbies and interests with the readers.*

A I enjoy traveling, especially to places of historical significance. They showcase the creativity and ingenuity of individuals of earlier eras, and I find that inspiring. I enjoy running and biking in the foothills and on the shores of Santa Barbara. They have inspired me to run more often and eventually led me to complete several half-marathons and a full marathon in southern California over the last couple of years.

Q *What career advice would you give to younger professionals starting in grad schools, industry, and academia?*

A My advice to young professionals is to nurture the spirit of creativity and innovation. The field is in constant need of creative, out-of-the-box ideas that can have a transformative impact. I think that the young professionals entering the field are in the best position to come up with such paradigm-shifting ideas; however, it takes a special effort to nurture the creative spirit, and the young professional should make that effort. ■

42ND CRS ANNUAL MEETING & EXPOSITION

July 26–29, 2015
Edinburgh, Scotland

CREATING VALUE THROUGH
CUSTOMISED DELIVERY

The CRS Annual Meeting brings renowned researchers, industry experts, and young scientists together from around the globe to discover customized approaches and high-value solutions in delivery science and technology. The dynamic exposition and targeted networking events are as carefully planned as the scientific content, making it easy to meet and discuss next steps to success.

Insights and Outlook: Plenary Speakers to Address Needs and Opportunities in Delivery Science and Technology

Complete presentation descriptions and speaker biographies available at **controlledreleasesociety.org/program**.

Polymers and Nanomedicines – The Promises and Pitfalls of New Materials

Cameron Alexander
School of Pharmacy, University of Nottingham, United Kingdom

Cameron Alexander is an Engineering and Physical Sciences Research Council (EPSRC) Leadership Fellow 2009–2014, professor of polymer therapeutics, and head of the Division of Drug Delivery and Tissue Engineering at the School of Pharmacy, University of Nottingham, United Kingdom. Research in his group centers on responsive materials for drug, gene, and cell delivery and new antimicrobial strategies. Prof. Alexander is also director of the EPSRC Centre for Doctoral Training in Advanced Therapeutics and Nanomedicines at the University of Nottingham and University College London with a number of leading pharmaceutical industry partners.

Global Efforts and Successes in Needle-Free Peptide Delivery

Maria José Alonso
Uniersity of Santiago de Compostela, Spain, and coordinator of the TRANS-INT European Consortium

Maria José Alonso is a full professor of biopharmaceutics and pharmaceutical technology at the University of Santiago de Compostela, Spain. She has made critical contributions to the design of novel nanostructures for the targeted delivery of drugs and vaccines and to the understanding of the interaction of nanoparticles with biological barriers. She is a member of several scientific and editorial boards and a director-at-large of the Controlled Release Society. She has received several awards, among them the Maurice-Marie Janot Award.

Ligand-Directed Therapy and Molecular Imaging Based on *In Vivo* Phage Display Technology

Renata Pasqualini
University of New Mexico Cancer Center, U.S.A.

Renata Pasqualini is a professor of internal medicine, the Maralyn S. Budke Endowed Chair in Cancer Experimental Therapeutics, and associate director for translational research and chief of the Division of Molecular Medicine at the University of New Mexico Cancer Center (UNMCC). She is an internationally recognized expert in vascular biology, metastasis, and angiogenesis. She originally codeveloped *in vivo* phage display and has been recognized for her contribution to identifying organ- and tumor-specific ligands to target vascular receptors. Her joint group has been working with phage display technology for nearly 15 years and has published extensively in this area.

42nd CRS Annual Meeting & Exposition continued on page 8

ANSWER THE CALL FOR ABSTRACTS THROUGH JANUARY 15, 2015

"This year's Call for Abstracts is organized around 10 core areas that represent the wide diversity of scientific and technical expertise in the delivery science arena. This new approach to organizing annual meeting content is designed to produce a balanced program while allowing greater flexibility in the creation of meeting content that reflects CRS member interests. We plan to offer meeting attendees expanded opportunities to exchange information on cutting-edge research, new technologies, and emerging growth areas."

Justin Hanes, Johns Hopkins University, U.S.A.
2015 Annual Meeting Program
Committee Chair

Bioactive Materials

Consumer & Diversified Products (C&DP)

Preclinical Sciences & Animal Health (PSAH) Applications

SUBMIT TO 10 CORE AREAS

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

For complete topic descriptions, please visit **controlledreleasesociety.org/abstracts**.

AMPC DEVELOPS

20 SCIENTIFIC SESSIONS

Following the call for abstracts, the Annual Meeting Program Committee (AMPC) will develop 20 scientific sessions that reflect CRS member interests, offer greater industry participation, and allow more time for questions and answers.

NEW! 90-minute scientific session format moderated by a CRS Fellow

40 minutes	Two Invited Speakers: 1 from industry, 1 from academia
30 minutes	Research Highlight Talks: 5 chosen from submitted abstracts *Speakers will prepare a corresponding poster presentation*
20 minutes	Q&A Session with All Speakers

The annual meeting experience will also include

Industry participation in the exposition hall, Technology Forums, and Soapbox Sessions

Invited speakers in five mini-symposia

Premeeting workshops

Poster presentations

College of Fellows Panel

Roundtable discussions

Young scientist programming

Targeted networking events

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EARLY EXHIBIT RATE ENDS JANUARY 31, 2015

Attendees say why they attend the CRS Annual Meeting

88%	Networking and making new contacts
88%	Learning about new technology
84%	Presenting new research
77%	Creating new business opportunities

July 26–29, 2015

Edinburgh International Conference Centre

controlledreleasesociety.org/meeting

EICC Photo by David Barbour

Investigation of the Permeability, Stability, and Toxicity of a Food-Derived Antihypertensive Peptide

John P. Gleeson, Joanne Heade, Sinead M. Ryan, and David J. Brayden
School of Veterinary Medicine and Conway Institute, University College Dublin, Belfield, Dublin, Ireland

Introduction

Ile-Pro-Pro (IPP) is a bioactive peptide found in bovine milk when casein is hydrolyzed by gastrointestinal enzymes. It has an angiotensin-converting enzyme inhibitory potency of 5µM with the potential to reduce blood pressure, if orally administered.[1] Although IPP is stable in intestinal fluids and against Caco-2 cell brush-border peptidases, it has poor intestinal permeability,[2] which is the limiting factor in converting it to an oral dosage form. A particular challenge is to find a safe and reversible enhancer to improve epithelial permeability when formulated with peptides and macromolecules. A route of intestinal permeation of IPP may be via the PepT1 carrier, so IPP could be a target for intracellular peptidases. The application of permeation enhancers on the permeability of oral drugs has shown significant results in numerous publications.[3] Few publications investigated cellular toxicity of IPP.

The hypothesis was that formulation of IPP in a nanoparticle may localise it near the intestinal wall and increase flux in the context of an incorporated enhancer. The objective of this study was to determine the stability of IPP in rat intestinal fluids and gut homogenates. The permeability of IPP was calculated across rat jejunum and colon mucosae *in vitro*. Also, the cytotoxicity of IPP in Caco-2 and Hep G2 cells was investigated. These data prepare the way for formulation into nanoparticles for oral delivery.

Experimental Methods

Stability of IPP in Homogenates and Gut Washes

A 25 cm section of duodenum/jejunum of male Wistar rats (250–300 g) was isolated. The section was flushed with 10 mL of simulated intestinal fluid (as per USP) to achieve a "gut wash." The washed section was placed in Hank's balanced salt solution (HBSS) and homogenized to yield "washed homogenate." Other sections were placed into HBSS and homogenized to yield "unwashed homogenate." IPP (4mM) and insulin (200µM) were incubated at 37°C and agitated at 200 rpm. Samples were taken at 0, 30, and 60 min and analyzed by RP-HPLC with the following C18 column gradient mobile phase: A, water 0.05% trifluoroacetic acid; and B, acetonitrile 0.05%. Samples were sourced from three rats and each run in triplicate.

Permeability Across Jejunum and Colon Tissue

Isolated muscle-stripped rat colonic mucosae and unstripped rat jejunal tissue from male Wistar rats were mounted in Ussing chambers. Fluorescein isothiocyanate (FITC)–IPP (500µM) was added to the apical chamber with the addition of 10mM of either sodium caprate (C10) or a novel medium-chain fatty acid derivative (10-undecylenic acid, sodium salt, uC11).[4] The apparent permeability (Papp) and transepithelial electrical resistance (TEER) were measured over 120 min. Tissue was sourced from five rats.

Cytotoxicity of IPP Using MTT and MTS Assay

Caco-2 and Hep G2 cells were cultured and seeded on 96-well plates in 200 µL of Dulbecco's modified Eagle's medium (DMEM) at 37°C. After 24 h, DMEM was removed and replaced with DMEM with IPP (0.1–10mM) or Triton®-X-100 (0.05%) for 1 or 24 h (Caco-2) or 72 h (Hep G2). Cells were treated with MTT or MTS accordingly. All data were analyzed by one-way ANOVA with Dunnett's post-test.

Results and Discussion

Incubation of IPP in rat intestinal homogenates and washes showed no evidence of metabolism over 60 min, confirming stability (Figure 1A). Enzymatic capacity of the three systems was confirmed by breakdown of human insulin (Figure 1B). The greatest capacity for metabolism of insulin was the gut wash

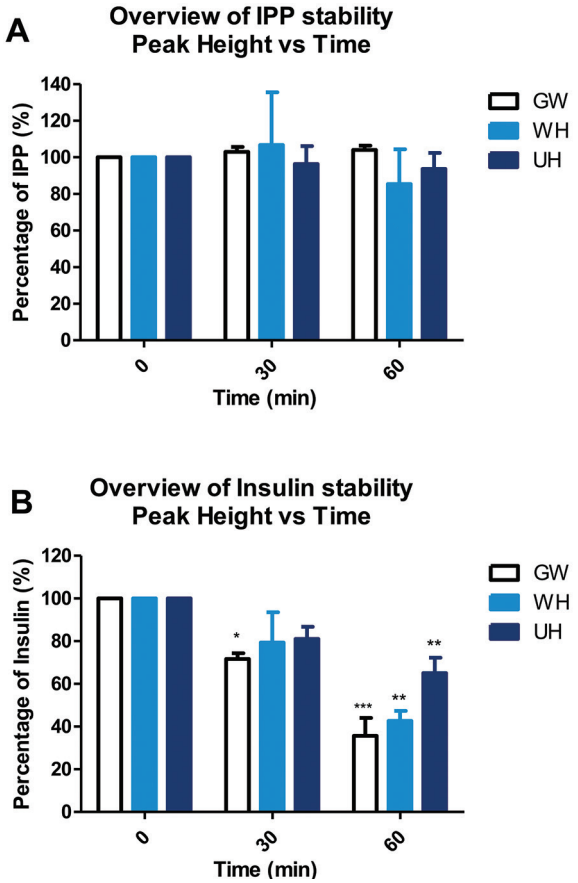

Figure 1. *Stability of IPP (4mM) (A) and insulin (200µM) (B) in rat gut wash (GW), washed intestinal homogenate (WH), and unwashed intestinal homogenate (UH). n = 3; *, **, and *** indicate P < 0.05, 0.01, and 0.001, respectively, compared with control (time 0). Each value represents the mean ± SEM.*

Scientifically Speaking Gleeson continued on page 12

Scientifically Speaking Gleeson continued from page 11

system, which broke down over 60% in 60 min, compared with 40% with the unwashed homogenate.

Permeation of FITC-IPP (Figure 2) was slightly higher but not statistically significant in jejunum compared with colon, perhaps because of the higher presence of PepT1 in jejunum. C10 and uC11 increased the Papp of IPP significantly. In parallel, both enhancers significantly ($P < 0.001$) reduced the TEER from 40 min in jejunum and within 5 min in colon (Figure 2).

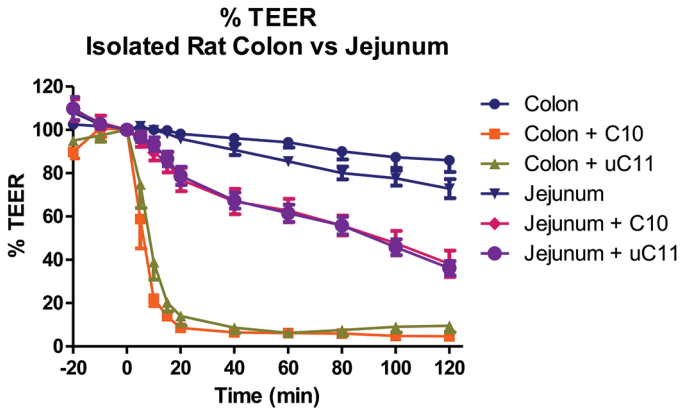

Figure 2. *Effect of enhancers on %TEER in isolated jejunal and colon mucosae. C10 and uC11, n = 5. Concentrations were 10mM in each case. Each value represents the mean ± SEM.*

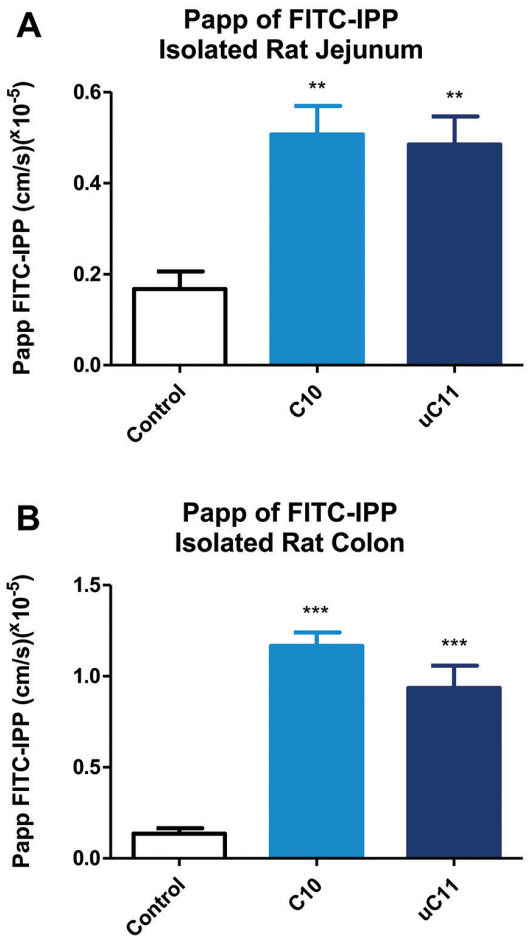

Figure 3. *Effect of the two enhancers on Papp of FITC-IPP in jejunal tissue (A) and colon mucosae (B). n = 5; ** and *** indicate P < 0.01 and 0.001, respectively, compared with control. Each value represents the mean ± SEM.*

Papp of FITC-IPP was significantly increased by medium-chain fatty acid type enhancers in jejunum (Figure 3A) and colon (Figure 3B). These data suggest that the tight junctions are being opened, thereby allowing FITC-IPP to permeate.

Comparison of the MTS and MTT cytotoxicity assays indicated that IPP was not cytotoxic in colon (Caco-2) or liver (Hep G2) cells, even at high concentrations of 10mM for 72 h (Figure 4). This was in agreement with previously published studies performed on CHL cells.

Conclusions

The milk-derived peptide IPP was stable in rat intestinal gut washes and homogenates and was noncytotoxic to human intestinal and liver cells. However, the limiting factor for oral

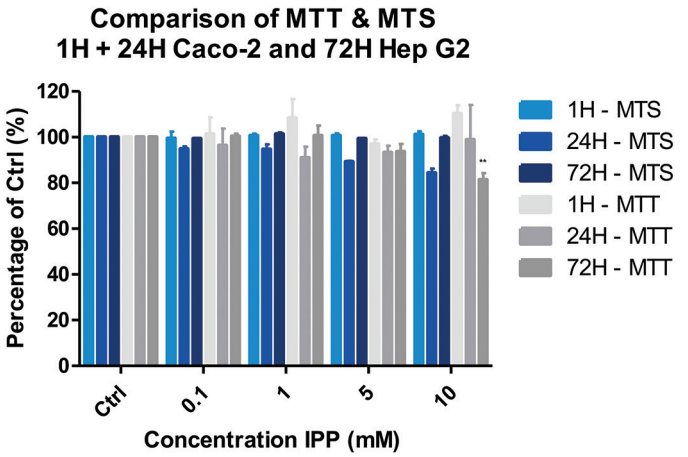

Figure 4. *Cytotoxicity analysis of IPP after 1 and 24 h incubation with Caco-2 and 72 h on Hep G2 cells. n = 3; ** indicates P < 0.01 compared with control. Each value represents the mean ± SEM.*

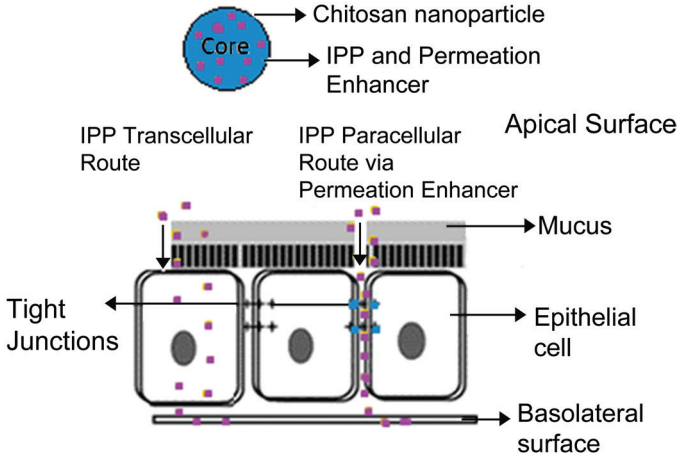

Figure 5. *IPP nanoparticle formulation and possible routes of transport. IPP (purple) and permeation enhancer (blue).*

peptide delivery is low intestinal permeability. Permeation enhancers C10 (which is currently in clinical trials) and uC11 (which is used in alternative medicine), were tested successfully with IPP in isolated rat intestinal tissue. This paves the way to investigate the potential of these enhancers in an IPP "nano" construct to potentially reduce blood pressure (Figure 5).

Acknowledgements
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Can Immobilised Lipase Be Used for Improving the Understanding of Lipid-Based Formulations for Poorly Water-Soluble Drugs?

Stephanie Phan,[1] Stefan Salentinig,[1] and Ben J. Boyd[1,2,3]

Introduction

Lipid-based formulations are of interest for the delivery of poorly water-soluble drugs. During the lipolysis of triglycerides, monoglycerides and fatty acids are produced. These combine with endogenous amphiphilic molecules in the gastrointestinal tract to form bile salt/phospholipid mixed micelles and other liquid crystalline phases.[1] These structures are important in maintaining drug solubilisation in the gastrointestinal environment, leading to enhanced absorption and bioavailability of coadministered drugs (Figure 1).[2,3]

In vitro lipolysis experiments using a pH-stat apparatus are frequently utilised to evaluate digestion of lipid-based formulations to examine drug disposition, solubilisation, and precipitation, with the aim to achieve *in vitro–in vivo* correlations. The current protocol for *in vitro* digestion studies utilizes porcine pancreatin extract[4–7] as the lipase source to simulate digestion in the small intestine. However, there are many proteins and enzymes in the crude extract that contribute to a high level of undesired scattering from pancreatic components, when using techniques such as small-angle X-ray scattering (SAXS)[4,8] and dynamic light scattering to understand the structural evolution caused by lipolysis products in these systems. These may obscure scattering from colloidal species produced on digestion and complicate the resolution of structures that are present.

Immobilised lipases are widely used as biocatalysts in the food, detergent, textile, cosmetic, and pharmaceutical industries, including the hydrolysis of triglycerides to produce fatty acids.[9] In the context of *in vitro* lipolysis experiments, having the enzyme immobilised on beads will enable separation from the digesting medium, which may improve the ability to study structural aspects using scattering methods, as well as provide an opportunity to simplify and standardize the *in vitro* test compositions. Consequently, in this investigation, lipase immobilised on polymer beads was evaluated as an alternative to powdered pancreatin during lipolysis.

Experimental Methods

The enzyme activity was determined using the pH-stat method, with 6 g of tributyrin[5,10] dispersed in 10 mL of digestion buffer for immobilised lipase or 9 mL of digestion buffer for pancreatic lipase, respectively, which itself was dispersed in 1 mL of buffer, and the fatty acids produced were titrated with 0.6M NaOH. The activity was defined in tributyrin units (TBU); 1 TBU is the amount of enzyme used to liberate 1 µmol of titratable free fatty acid per minute. The immobilised lipase was Novozym® 435, a commercially available recombinant lipase B from *Candida antarctica* manufactured by Novozymes.[11,12]

For the medium-chain triglyceride (MCT) digestion experiments, tricaprylin or Captex 355 was added to fasted simulated intestinal fluid (prepared in digestion buffer with bile salt [sodium taurodeoxycholate] and phospholipid [1,2-dioleoyl-*sn*-glycero-3-phosphocholine] at concentrations of 5mM:1.25mM) in the thermostatted digestion vessel at 37°C and digested at pH 6.5.[13] On addition of lipase (~1,000 TBU/mL of digest) the pH-stat titrated the digestion medium with 0.6M NaOH to maintain pH 6.5 ± 0.003. Digestion was allowed to proceed for up to 8 h, in which the degree of enzymatic digestion of the lipid was reflected in the volume of NaOH used to neutralize the fatty acids liberated during the digestion process. Production of fatty acid was also followed using HPLC on samples of the digesting mixtures.[14]

SAXS measurements on endpoint digestion samples of MCT were performed at the SAXS/WAXS beamline[15] at the Australian Synchrotron in quartz capillaries, with buffer subtracted as constant background.

Results and Discussion

Lipolytic Activity

Activity of the immobilised lipase was very different to that of the pancreatin extract. The immobilised lipase displayed a linear dependence on the mass of enzyme used (Figure 2A). In contrast, the activity per milligram of pancreatic lipase decreased with increasing concentration. So in addition to being more predictable in its measured activity against tributyrin, it was also more active on a per mass basis at higher levels of lipase. Pancreatic lipases are interfacial enzymes, operating at an oil–water interface, whereas it is difficult to conceptualise an interfacial dependence for an immobilised enzyme. Additional studies showed that the enzyme was definitely immobilised on the surface, hinting that the reactivity of the immobilised enzyme may be higher toward tributyrin in solution, rather than tributyrin at an emulsion interface.

The activity of the immobilised lipase was dependent on temperature (Figure 2B), as reported in the product information; however, it was still highly active at 27°C, which is significant, because the highly convoluted *in vitro* models used in the assessment of lipid-based formulations dictate that the reaction

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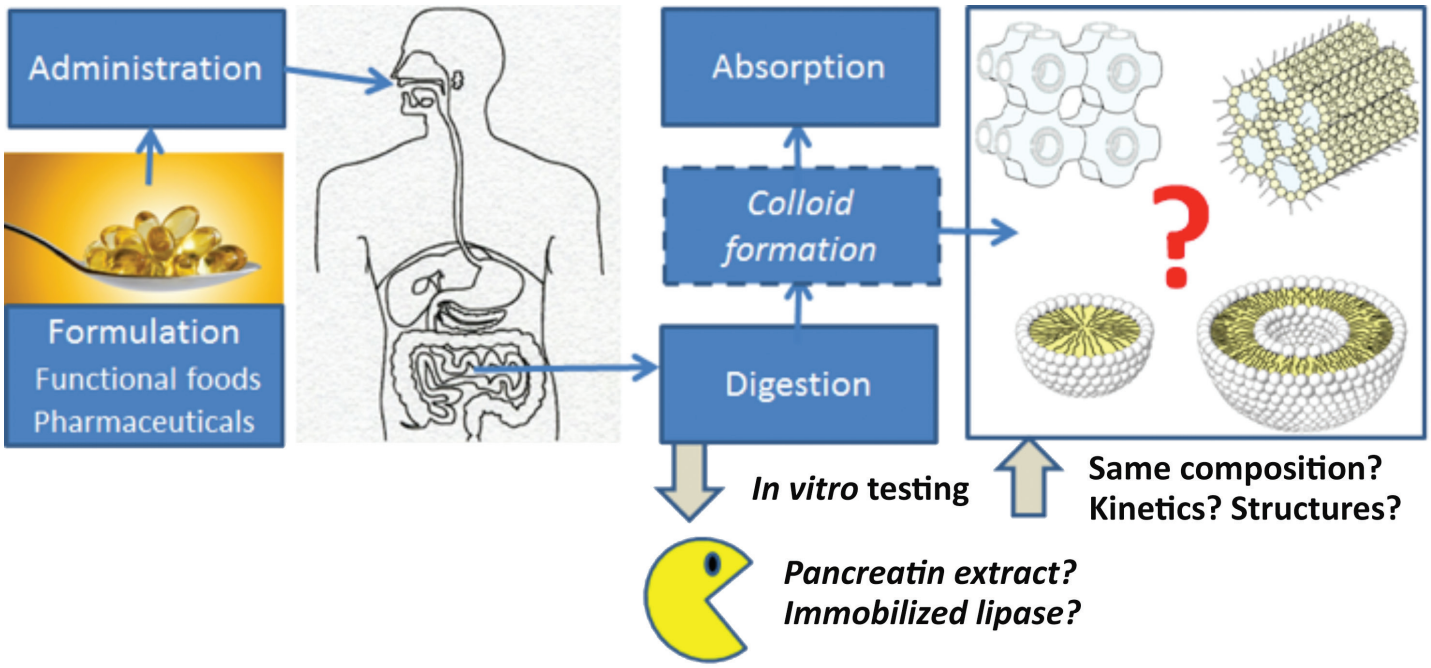

Figure 1. *Lipid-based formulations can facilitate the absorption of poorly water-soluble drugs in part through formation of colloidal structures in the gastrointestinal tract on digestion of the lipid components.*

be conducted at physiological temperature. It may not be necessary to do this in the case of immobilised lipase, however, because addition of additional lipase would provide the same outcome in terms of activity. No significant buffer or pH dependency was observed on the activity (Figure 2C and D).

In Vitro *Lipolysis of MCTs*

The kinetics of digestion of tricaprylin and Captex 355 using the immobilised lipase was dramatically slower when compared with the pancreatic lipase at the same activity. A much longer digestion time was required to achieve a plateau in the titration curve (Figure 3A and B). Notably, the digestion profiles of Captex 355 for both the lipases had a sigmoidal shape but covered very different time scales. There was a strong correlation between the moles of fatty acid liberated during lipolysis by the two enzymes as determined by pH-stat titration and HPLC (Figure 3). At the endpoint of digestion, the fatty acid content was determined by HPLC to be 92.7 and 90.6% for pancreatic and immobilised lipase, respectively. The difference in timescales may be explained by the likely poor access of the immobilised lipase to the triglyceride substrate: in the case of much more hydrophobic MCT lipids, digestion of material from solution, rather than at the interface, would be expected to limit the activity of the immobilised lipase compared with pancreatin,[16] which is consistent with the findings here.

To determine whether separation of immobilised lipase from the digestion medium would be sufficient to halt digestion, samples were removed at predetermined time points, without addition of the commonly used inhibitor, 4-bromophenylboronic acid (4-BPBA). Correlation of fatty acid content by HPLC and

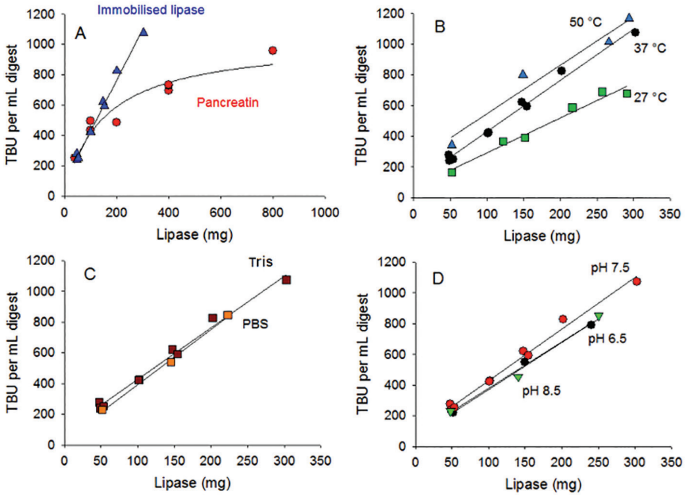

Figure 2. *Effect of reaction variables on activity of lipases. (A) Immobilised lipase versus pancreatin with increasing mass of lipase added to the reaction. (B–D) Effect of reaction variables on activity of immobilized lipase: (B) temperature; (C) buffer type (Tris versus PBS) at pH 7.5 at 37°C; and (D) buffer pH (Tris buffer pH 6.5, 7.5, and 8.5 at 37°C). TBU = tributyrin units.*

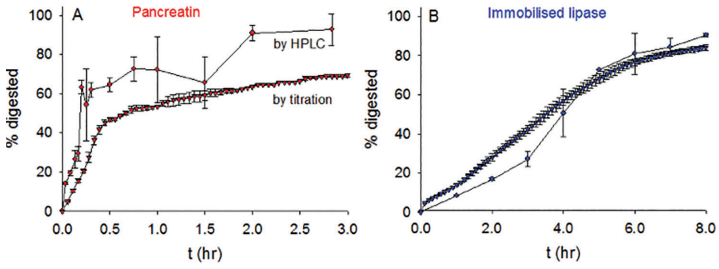

Figure 3. *Kinetics of digestion during lipolysis of ~50mM Captex 355 in the fasted state at 37°C with (A) pancreatin and (B) immobilised lipase, showing fatty acid determined by HPLC (circles) and titration (triangles). Data are mean ± range (n = 2).*

Scientifically Speaking Phan continued on page 16

Scientifically Speaking Phan continued from page 15

pH-stat titration again was observed, confirming that the lipase remained adsorbed to the polymer beads rather than leaching into the digestion medium. Consequently, unlike pancreatic lipase, inhibition with a molecular inhibitor such as 4-BPBA is not required.[8]

Structure Formation During In Vitro *Lipolysis*

Synchrotron SAXS measurements showed that although both digestion media contained lamellar phases with identical structures, evident from the evenly spaced peaks in *q* and consistent with previous flow-through digestion experiments on this system,[8] a significant order of magnitude reduction in the scattering was observed in the system digested by immobilised lipase compared with pancreatic lipase (Figure 4). The decreased parasitic scattering observed during lipolysis with immobilised lipase renders it a better lipase for structural studies. Application to time-resolved structural determination through improved quality of scattering data is expected to now be enabled by this discovery.

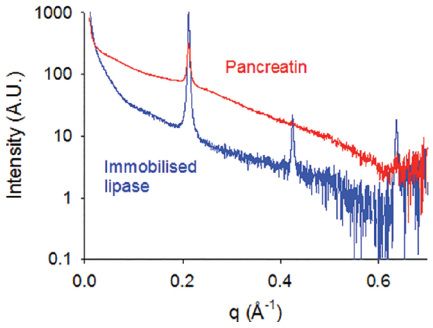

Figure 4. *SAXS profiles of end point of lipolysis of 50mM Captex 355 in the fasted state at 37°C. Lipolysis was performed with pancreatin (upper) and immobilised lipase (lower).*

Conclusion

This is the first description of immobilised lipases being used for *in vitro* lipolysis. Immobilised lipase is an interesting alternative to powdered pancreatin in *in vitro* lipolysis experiments, in which interrogation of self-assembled structure is important. The structural and compositional changes during *in vitro* lipolysis were maintained regardless of lipase used; however, the decreased background scattering observed with immobilised lipase renders it advantageous over lipase sourced from porcine pancreatic extract for understanding structure formation during lipolysis. Although the kinetics of digestion of formulation lipids was slow, its activity was independent of pH; hence, it could be used with phosphate-buffered saline (PBS) as a simplified buffer system. It maintained moderate activity at ambient temperature, indicating that immobilised lipase may also find application in a significantly simplified approach to *in vitro* lipolysis studies.

Acknowledgements

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

Compiled and Edited by Terry Bowersock[1] and David Brayden[2]

Cyanide toxicity can cause potentially fatal cardiac, neurological, and metabolic disturbances in humans. Better antidotes to cyanide are needed even though the biological processes affected are not known. Nath *et al.* developed a zebrafish model to improve understanding of the metabolic effects of cyanide and to screen potential antidotes using zebrafish as a high-throughput model.[1] Over 3,120 chemical entities were screened, with four showing potential to neutralize cyanide in the zebrafish. Metabolomic profiling of the zebrafish also revealed changes in bile acid and purine metabolism. Riboflavin was found to be the most effective antidote in mitigating the neurological and metabolic changes induced by cyanide in the zebrafish. Riboflavin was also the safest therapy, as the three other compounds—cisplatin, carboplatin, and methotrexate—are chemotherapeutic agents with known side effects. The results in the zebrafish were confirmed in a rabbit model, and metabolic changes seen in the zebrafish were consistent with those seen in humans with cyanide toxicity. The zebrafish was found to be an excellent model to study cyanide toxicity and an effective way to screen potential therapeutic agents.

The ability of adult urodele amphibians such as salamanders to regenerate fully functional limbs is well known, but the factors involved in this process have been unknown. To elucidate this wound-healing ability, Mu *et al.* used skin from the salamander *Tylototriton verrucosus* to extract a wound-healing and skin-regeneration peptide called tylotoin.[2] Skin extracts were subjected to gel filtration and high-performance liquid chromatography and then placed on keratinocytes and endothelial cells to determine their response to the products of the extraction. Further structural and functional assays were done to identify a short peptide as a potent stimulant of skin regeneration. Tylotoin belongs to the cathelicidin proteins, which are highly conserved across vertebrates and when enzymatically processed release antimicrobial peptides. Similar to these peptides, tylotoin is located at the C terminus of cathelicidin. Although it does not have antimicrobial activity, tylotoin peptide was found to have similar wound-healing capabilities as epidermal growth factor. Tylotoin activates the migration and replication of keratinocytes, vascular endothelial cells, and fibroblasts required for new epithelium to form. When tested in full dermal lesions in mice, tylotoin stimulated accelerated reepithelialization and granulomatous tissue generation at the wound site. Tylotoin is 12 amino acids in length and could readily be cloned to generate a potent skin-healing compound. This peptide may explain how reepithelialization takes place in a mere 10 h in salamanders compared with 2–3 days in mammal skin lesions. Tylotoin stimulates transforming growth factor B1 and IL-6 release needed to repair skin wounds. Several genes have previously been identified as important for skin healing and limb regeneration in amphibians, but no factors have been identified up to this point. Because one of the first steps in limb regeneration is reepithelialization, this compound could be very useful in the healing of wounds in other species than urodele amphibians.

Rabies is caused by a virus shed in the saliva of rabid animals. Worldwide, 69,000 humans die from rabies contracted from an animal bite. The virus spreads to the central nervous system, causing inflammation and death. Most of these deaths occur in Africa and Asia, with one third of the deaths in India alone, with 40% of cases in children. Lankester *et al.* note that the actual number in these countries may be 20–160 times higher, because most people never make it to a medical facility or report the disease.[3] Most of these cases could have been prevented by routine vaccination of dogs, which is routinely done in developed countries. Prevention of human cases by vaccination of dogs is highly successful, and prevention is cost effective. Vaccination of 70% of dogs in an area is highly cost effective in reducing human cases. Postexposure treatment requires a series of painful injections of exposed individuals. In remote areas or poor countries, these treatments are not always readily available, are expensive, and must be given over a two-week period. Rabies has been nearly eliminated in developed countries by routine vaccination of dogs and use of aerial distribution of baits containing rabies vaccine to control rabies in wildlife. Reduction in dog numbers has not proven to be as effective a method to control rabies as vaccination. A recent concerted dog vaccination program in Tanzania reduced the number of human cases to near zero in an area 10,000 km^2. There has been success as well in reducing rabies in South Africa and the Philippines. The tools are available to eradicate rabies worldwide but require a coordinated global political commitment to do so. This has been lacking and continues to be a leading reason for the persistence of rabies. Without the postexposure injections, exposed individuals are highly likely to die. The International Federation of Animal Health celebrated World Rabies Day on September

1 Zoetis, LLC, U.S.A.
2 University College Dublin, Ireland.

28, 2014, to call for a global One Health effort to dramatically reduce human rabies cases on several fronts including improving vaccination programs, disease surveillance, and diagnostics as well as encouraging responsible pet ownership. Without an effort to control it, rabies will continue to be the most untreatable fatal disease of humans and a threat to half the world population.

Ninety percent of cancer drugs fail after promising results in mice.[4] This is especially disturbing for pancreatic cancer, for which the five-year survival rate in humans is 6%. Better predictive mouse models are needed to screen chemotherapeutic agents. Efforts are expanding to develop better mouse models. For many years the standard model was to grow human cancer cells *in vitro*, inject them into mice, and evaluate therapeutic agents in the mice. Now more sophisticated models are being developed. One centers on creating the same genetic mutations in the mice, targeting the Kras gene present in 95% of human pancreatic tumors and the p53 gene present in 70% of tumors. For pancreatic cancer, this translates into the mutations leading to development of tumors in the mouse pancreas. As in humans, the pancreatic tumors metastasized to similar organs—liver, lymph nodes, and lungs. Histologically, lesions even looked similar to human tumors. The mouse model was tested with a drug that had performed well in mice but that only 5–10% of humans responded well to; the mice in this new model responded similarly again to humans. However, when the mouse model was used to test a novel human drug, positive results in the mice raised the expectation for success in humans only to fail miserably. Further evaluation of the model identified that the drug affected the stroma of tumor but allowed cancer cells to mutate and replicate unperturbed, and the mouse model showed efficacy after two weeks in mice, whereas the human trial lasted six months. When the model was repeated in mice for a longer duration, four months, the drug performed similarly to humans. So it appears the model does have a future, but it shows how critical matching the model to the disease can be. Other approaches to novel mouse models include the patient-derived xenograft (PDX) model in a patient-personalized model approach. Mice are injected with tumor cells from one human patient. In this model, over time, the human tissue stroma is replaced by mouse tissue, theoretically providing scientists with a more humanlike mouse response to therapeutic agents targeted for a specific tumor. However, in this model, the mice are immunodeficient, so monoclonal antibody-based drugs cannot be tested, and the model takes time to be developed and generate data, time that many cancer patients do not have. These models have generated hope that newer novel models will lead to better evaluation of novel cancer drugs for patients.

Progesterone has been the only member of the progestin class identified and characterized by its ability to maintain pregnancy in horses, humans, and most mammalian species. However, despite this association, in horses (as well as zebras, humans, hyrax, and elephants, for example), pregnancies have been known to be completed despite no detectable progesterone in the body. Another progestin has been suspected to be present in these cases, but none was identified until recently. A study by Scholtz *et al*. identified 5α-dihydroprogesterone (DHP) as a progestin made at the expense of progesterone levels but retaining its ability to bind to progesterone receptors (PR) that can maintain physiological changes in the uterine endometrium *in vitro* in a manner similar to progesterone, sustain pregnancy in ovariectomized horses at times when progesterone is undetectable, and induce expression of progesterone responsive genes *in vitro*.[5] It also can bind to human PR to a level suggesting it can also sustain human pregnancy as well, based on levels present in the third trimester. This has been a puzzling question for five decades—how pregnancies can be sustained when progesterone levels are no longer detectable. This also suggests that there may be other sex steroids across mammalian species that have not yet been discovered.

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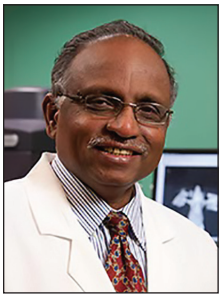
The Impact of "Negative Data"

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

"Negative results are just what I want. They're just as valuable to me as positive results. I can never find the thing that does the job best until I find the ones that don't."
– Thomas A. Edison


Vinod Labhasetwar

There is an ongoing debate on the value of publishing (and the effects of withholding) negative research results. I discussed this very point during the meeting of the editorial board for *Drug Delivery and Translational Research* (*DDTR*) held during the 41st CRS Annual Meeting in Chicago this past July. There, the board members agreed that *DDTR* should consider manuscripts reporting negative data, as long as the research is based on a strong rationale or hypothesis.

We all know that not all experiments lead to expected or positive results, nor are all proposed hypotheses correct. Oftentimes, we encounter more failure than success, but we report only positive results simply because it is hard to publish negative results. I can give you an instance from my own experience. The study was part of a peer-reviewed, federally funded grant carried out about 20 years back. The experiment was to test a time-release capsule following oral delivery. We tested this capsule in rabbits, simply because we thought we could easily draw blood multiple times in sufficient quantities through an ear vein to analyze drug levels to show time-release drug profile. The other reason was that we could easily feed a regular-sized capsule used in humans to rabbits, which for a study in rats would have required miniaturizing the size.

Why did this experiment fail? Because gastric emptying time in rabbits is significantly longer than in rats or humans. The rabbit stomach can retain a significant amount of food, even after 24 h of fasting. Our capsule had been designed to withstand gastric pH for a few hours and then open up in the small intestine at a different time interval. In this experiment, we could detect the intact capsule retained in the rabbit stomach even after one full day. Because the capsule was retained in the acidic pH for so long, it failed to function as expected. The important lesson to be learned, for our own and others' investigations, was that the rabbit is not the best animal model in which to test oral time-release or sustained drug delivery systems. Yet we could not publish the study results because of the "negative" outcome.

The scholarly debate has led to at least one attempted solution: the online, open-access publication *Journal of Negative Results in BioMedicine* (BioMed Central; the editor-in-chief is Bjorn Olsen of Harvard). And while our own *DDTR* will retain its main purpose as a vehicle for all translational aspects of drug delivery, we on the editorial board recognize that our readers could benefit from the publication of negative results and from reports of what approaches did not work as expected. If methodological or logistical flaws of a research path are quickly brought to light, other investigators may not continue down that same ineffectual path, and in the end, funding and valuable laboratory resources will be better used. If one group reports negative findings, there may be a useful learning curve for us all based on that negative data, so that others might get novel ideas in terms of revising their hypotheses or experimental designs. For some, negative data from one study could provide a rationale or new approach/paradigm to pursue. It is well known that many experiments work well *in vitro* but not *in vivo* or fail to demonstrate efficacy in preclinical testing. Unexpected toxicity may limit the benefits of a drug or a particular mode of delivery. Reporting negative data from clinical trials is clearly essential, because it can have a direct impact on human health.

From now on, *DDTR* will consider manuscripts that report negative results. Such manuscripts will undergo the standard, rigorous review process, but the reviewers will be alerted to the nature of the manuscript. Authors are strongly encouraged to discuss the possible reasons why experiments failed and what alternative approaches or changes to the hypothesis or experimental design might be made.

We expect that this new editorial policy will enhance *DDTR*, making it an improved tool for all of us in the drug-delivery field. We welcome your views, pro or con, and look forward to hearing from you.

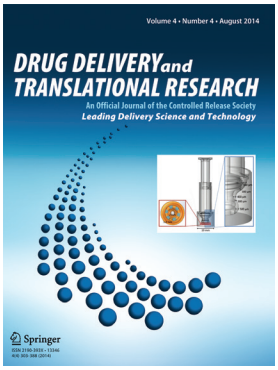
***DDTR* Special Issue: Call for Papers**

DDTR is accepting submissions for a special issue on **Orthopedic Biomaterials and Drug Delivery**, which will showcase emerging pharmaceutical and regenerative approaches to treat injuries, diseases, and disorders of the musculoskeletal system. Topics include gene/drug delivery systems, cell-based therapies, and biomaterials to support orthopedic tissue regeneration and/or disease modification. Deadline for submission is January 15, 2015. Guest editors are Blanka Sharma (blanka.sharma@bme.ufl.edu) and Shyni Varghese (svarghese@eng.ucsd.edu).

Editor's Choice (Vol. 4, Issue 4)

Rapid Reconstitution Packages (RRPs) implemented by integration of computational fluid dynamics (CFD) and 3D printed microfluidics

Albert Chi, Sebastian Curi, Kevin Clayton, David Luciano, Kameron Klauber, Alfredo Alexander-Katz, Sebastian D'hers, and Noel M. Elman



This paper describes the design of Rapid Reconstitution Packages (RRPs), a portable platform that integrates microfluidics for rapid reconstitution of lyophilized drugs. RRPs were designed using computational fluid dynamics techniques to optimize fluidic structures for rapid mixing, integrating physical properties of targeted drugs and diluents. Devices were manufactured using stereo lithography 3D printing for micrometer structural precision and rapid prototyping. Reconstituting lyophilized drugs is an operational challenge in demanding environments, for example, disaster zones, battlefield support, and rural areas. Device performance was evaluated by selecting tissue plasminogen activator (tPA), which is unstable in liquid form, as the initial model drug. tPA is a commonly used thrombolytic for treating ischemic stroke and myocardial infarction, which are often emergency situations.

***DDTR* Outstanding Research Paper Award**

Consider submitting your best research for the 2015 *DDTR* Outstanding Research Paper Award. The paper will be selected from the research articles, clinical research, and clinical trials published in *DDTR* during 2015 and will be presented during the 43rd CRS Annual Meeting, July 17–20, 2016, Seattle, Washington, U.S.A. Visit the CRS website for award criteria.

Visit the *DDTR* website to glance through research articles, reviews, editorials, and special issues published in *DDTR*. CRS members receive free access to the journal content as a membership benefit. Login to the CRS website first, and then click the Publications tab to get to the member access link. ■

Animal Health Experts Meet to Learn and Network

Nearly 60 attendees gathered in San Diego, CA, U.S.A., to attend the CRS–AAPS joint Animal Health Drug R&D: Formulation, Delivery & Development to Market workshop prior to the AAPS Annual Meeting. This workshop was created by members of the CRS Preclinical Sciences & Animal Health (PSAH) Division and featured case studies, pharma testimonials, university research, and regulatory perspectives. Attendees heard about novel formulations, medical devices, drug–device combinations, and taking veterinary therapeutic concepts to the commercial market. CRS thanks the following sponsors for funding speaker travel: Peter Cremer North America, Scynexis, and Zoetis. ■

Speakers pictured front row: Wendy Collard (Zoetis), Jane Owens (Elanco), Mai Huynh (FDA), Marilyn Martinez (FDA), and Izabela Galeska (Merial). Second row: Shoban Sabnis (Zoetis), Dan Peizer (Catalent), Raafat Fahmy (FDA), Anthony Listro (Foster Corp.), Michael Putnam (Boehringer Ingelheim Vet Medica, Inc.), Brian Carlin (FMC), Robert Zolynas (Bayer Healthcare), David Brayden (University College Dublin), Praveen Hiremath (Bayer Animal Health), and Kaushalkumar Dave (South Dakota State University).

Volunteering: A Way to Connect, Build, and Change

"*Volunteers do not necessarily have the time; they have the heart*," reads the well-known quote by Elizabeth Andrew. And indeed the essence of this quote is clearly evident in the passion displayed by CRS volunteers for the successful management of this organization. Even as we are reading this section, a dedicated team of CRS volunteers is already working toward finalizing the content and planning of various events for the forthcoming CRS Annual Meeting & Exposition that will take place in 2015 in Edinburgh, Scotland. Needless to say that participation in such activities is a win-win situation for the volunteers too. Volunteering has helped these individuals widen their own networks and enhance their professional, social, and relationship skills, and it has had an overall positive impact on their careers. The volunteers featured in earlier Volunteer Spotlights have highlighted these benefits.

In this article, we introduce two more volunteers through their dialogues with Volunteer Recruitment Committee (VRC) member Prajakta Dandekar Jain. **David Chen** shares his experiences of working with various CRS committees, and **Medha Joshi,** who has recently joined the "volunteer family," sheds light on her motivations and expectations from being actively associated with the organization.

David Chen

David is a member of the novel drug delivery technologies team at Pfizer and is based in the Boston area. He earned his Ph.D. in chemical engineering from Cornell University and was previously a postdoctoral scientist at Novartis in the vaccines delivery and formulations group. David is currently serving as deputy chair of the CRS Young Scientist Committee (YSC) and is also a member of the VRC.

Q *How long and in what capacities have you been associated with CRS?*

A I have been a CRS member since I was a graduate student some years ago. I attend the annual meetings as often as I can and will also occasionally chair a YSC event. Over time, I have begun to take on a more active role on the CRS committees, and currently I am deputy chair of the YSC and also a member of the VRC.

Q *Tell us about your experiences as a CRS volunteer.*

A I have really enjoyed being a volunteer for CRS. While the annual meeting is clearly the most visible element of CRS, a big part of CRS that society members don't often get the chance to see is the day-to-day inner workings of managing and running a worldwide organization, which happens quietly behind the scenes. Much of this is driven by staff and volunteers, and I see it as an excellent opportunity to play a role in influencing the direction of the society.

Q *You have worked as a member of diverse committees comprising both budding and experienced volunteers, including the YSC and VRC. How do you think the activities of these committees have helped in engaging additional students and young scientists as CRS volunteers?*

A In my role as deputy chair of the YSC, I assist the committee chair (Patrick Lim Soo) in supporting and leading the committee's work. The YSC is responsible for programming the Young Scientist events at the annual meeting to support students and early career professionals, as well as leading the Mentor/Protégé Program. I really enjoy working with the energetic and enthusiastic committee members. I have always been interested in education, outreach, and early career development, and these interests are in tune with the goals of the YSC. I was a grad student not very long ago, and I really benefited from participating in CRS Young Scientist programs in the past, so I see this as an opportunity to return the favor.

My committee roles on the VRC and the YSC are complementary to each other. Louise Rosenmayr-Templeton and Arlene McDowell have done a fantastic job getting the committee off the ground and running. The VRC is focused on developing tools and resources to assist the society in recruiting volunteers and matching volunteers' interests with the needs of the specific committees. As I see it, the YSC in the past has been an unofficial entry point to CRS volunteering for many students and postdocs, and we see a lot of future opportunities for students, postdocs, and early career professionals in being volunteers with CRS, and not just on the YSC.

Q *How do you balance your schedule with your volunteering activities?*

A These days it is always a challenge to balance all the various demands on one's schedule. Unfortunately, I have not found a magic solution! It definitely takes organization and planning. Fortunately, all of my fellow committee members and volunteers are equally committed to the work. Our volunteers are scattered throughout the globe (which makes for some interesting meeting times), and although it sometimes involves the occasional late night or odd hours, it is always fulfilling to see the fruits of one's labors. I have many friends and colleagues who are equally active in CRS volunteer work, and although it is certainly serious work, it is important to remember to enjoy the journey as well.

Medha Joshi

Medha, a new VRC member, received her Ph.D. in pharmaceutics from the Institute of Chemical Technology, University of Mumbai, India, before conducting four years of postdoctoral research at the Free University of Berlin, Germany, and Utrecht University, the Netherlands. She then worked with Ocean Nanotech, U.S.A., on the production and development of diagnostic lipid-based nanoparticle systems. Currently, she is employed as an assistant professor in pharmaceutical sciences at Midwestern University's Chicago College of Pharmacy. Her research interests involve development of lipid-based drug delivery systems including microemulsions, liposome technology, and targeted drug delivery.

Q *What motivated you to take up volunteering for CRS?*

A CRS is the premier society in the field of delivery science and technology. I first joined the CRS local chapter as a graduate student and have attended the annual meetings since 2005. From the beginning, I have been impressed with the quality of the science presented at these meetings, including the plenary, posters, podium presentations, panel discussions, and so on. As my career progressed and I moved from India to Europe and then to the United States, my involvement in CRS became more frequent and my motivation to volunteer for CRS became even stronger. I have also been fortunate to work with eminent professors and scientists who are part of CRS; their example has further fuelled my motivation to be a part of CRS and contribute to the society.

Q *Tell us about your skills and the qualities that you think will help you to be an active volunteer with CRS.*

A The goal of the VRC is to implement programs for the sustainable recruitment of volunteers for a variety of CRS committees and activities. I have worked in a variety of cultures on three continents across the globe, and I will draw on that diversity of experience when recruiting volunteers from a range of sources and matching volunteers with tasks. I am aware that VRC committee work is sometimes time consuming, but my time-management skills will allow me to meet my other responsibilities while contributing as an active volunteer with CRS.

Q *Do you think this volunteering will contribute to your personal or career development? If so, how?*

A Yes, I absolutely think this will contribute to my career development. My experience serving on various college and university-wide committees has shown me that working with a committee is a great learning experience and an excellent opportunity to network with my peers. Although the work can be time consuming and demanding at times, the sharing of ideas is invaluable. Volunteering with the VRC will give me the ability to learn from and network with colleagues outside of my workplace, from around the globe. As I grow in my career, my VRC colleagues can help me, and I can help them, with advice, career mentoring, discussion of research questions, collaborations, and other topics.

Q *What are your expectations of being a member of the VRC?*

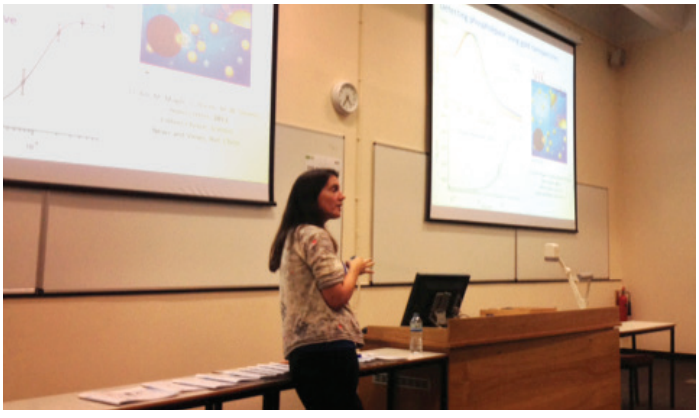
A As a member of the VRC, I will interact with volunteers and recruits for other committees, which will allow me to meet and work alongside a variety of people. I expect that I will learn skills and build relationships with mentors, colleagues, and students that will help me to grow personally and professionally and will enhance both my own work and my work with CRS.

Thank you, David and Medha, for sharing your personal views and experiences with our readers. We anticipate that your words will inspire many others to volunteer with CRS. ■

UKICRS Sessions Focus on Biomaterials in UK PharmSci on September 9, 2014

Maria Marlow,[1] Andrew Parker,[2] and Sion Coulman[3]

Biomaterials was the theme this year of the CRS UKI Local Chapter (UKICRS) sessions, and the first session chaired by Maria Marlow (University of Nottingham) was dedicated to cell responses at surfaces. Morgan Alexander (professor of biomedical surfaces at University of Nottingham) gave a talk focused on the chemical modification of surfaces to promote pluripotent stem cell differentiation. The methodology developed by his group is a combinatorial approach whereby thousands of monomer combinations can be screened using polymer microarrays. The microarrays are created using a contact printing robot and UV photopolymerisation and are then characterized with high-throughput methodologies using X-ray photoelectron spectroscopy, time of flight–secondary ion mass spectroscopy, and atomic force microscopy. The highlight of the talk was his recent unpublished work on developing a high-throughput cardiac toxicity screen, in which a polymer substrate influences the differentiation of pluripotent stem cells to cardiomyocytes. The second speaker of the session was Matt Dalby (University of Glasgow), and his presentation also focused on the biological response of cells to surfaces, specifically using nanoscale topography and mechanical properties to guide stem cell growth and differentiation. A focus of his work is bone tissue engineering, evaluating stem cell differentiation toward the production of bone. His most translational work is using nanotopography of titanium implants to stimulate bone growth, versus that of fibrobitic capsule formation leading to hip replacement failure. He also presented work on the influence of hydrogel rigidity to modulate stem cell differentiation to bone. The session also had contributions from young scientists Hoda Eltaher (University of Nottingham) and Shuai Wang (University of Loughborough), who presented work from their doctoral studies on directed stem cell differentiation and nutrient transport across tissue engineering membranes.



Invited speaker Molly Stevens from Imperial College London.

Speakers and the chair, Maria Marlow (right), in the first UKICRS session of the day.

The second session was chaired by Andrew Parker (Molecular Profiles) and had a focus on industrial application of biomaterials as part of the first two presentations. The first invited speaker, Andy Lewis (Biocompatibles/BTG), gave an insightful talk explaining the development of an embolic drug-eluting bead capable of loading and releasing, in a controlled manner, chemotherapeutic agents used in transarterial chemoembolisation (TACE). Andy Lewis explored the material properties of the biomaterial, a biocompatible polyvinyl alcohol (PVA) hydrogel that has been modified with sulphonate groups for the controlled loading and delivery of chemotherapeutic drugs such as doxoyrubicin. The bead acts to occlude the blood flow to the target tissue and delivers a local and sustained dose of drug directly to the tumour. The second invited speaker, Charlie Parkinson (GSK Healthcare), gave a talk summarising the historical development of the use of biomaterials in toothpaste to help protect, and even repair, damaged enamel where dentine is exposed that could lead to toothache. He showed in particular the use and application of calcium sodium phosphosilicate (Bioglass, Novamin), which can be used to help dentinal hypersensitivity (DH), a commonly encountered problem, and how bioglass physically occludes and adheres intimately to dentinal tubules to reduce sensitivity. Fang Liu (University of Hertfordshire) gave an interesting presentation showing the characterisation and cross-correlation of the permeability of ethylcellulose/hypromellose films analysed using transmuccosal water loss (TMWL) and Raman microscopy analysis, and a student of Joshua Boateng (University of Greewich) spoke about how plasticisers can be used to modify the hardness to different extents in hydroxylpropylmethylcellulose and sodium alginate based films for buccal mucosa drug delivery.

The final UKICRS session on biomaterials focused on the design and development of regenerative medicines using novel materials and pharmaceutical formulations. It was chaired by

1 University of Nottingham, United Kingdom.
2 Molecular Profiles, United Kingdom.
3 Cardiff University, United Kingdom.

Sion Coulman (Cardiff University). This session had four speakers: Molly Stevens, Kevin Shakesheff, Zeeshan Ahmed, and Judit Huarte. Molly Stevens (Imperial College London) focused her talk on the development of nanomaterials for protein sensing. She described the use of gold nanoparticles and nanostars in the development of high-sensitivity biosensing assays for the detection and quantification of a number of clinically relevant proteins in full serum samples. She also provided us with a glimpse into some exciting unpublished work on the development of nanomaterials for intracellular sensing. Kevin Shakesheff (University of Nottingham), director of one of five U.K. Regenerative Medicine Platform hubs, described the development of an innovative injectable microparticle formulation that can be used as a thermosetting scaffold in the delivery of both cells and drugs for regenerative medicine applications. He also discussed the development of a novel intracellular delivery system using cell-penetrating peptides and shared his plans to develop a trypsin-free method to manufacture cell therapies, which will hopefully accelerate the translation of cutting-edge regenerative medicine science to the clinic. The penultimate presentation by Zeeshan Ahmad (De Montfort University) focused on the development of a spray method to produce multilayered dressings, and the final speaker of the session, Judit Huarte (University of Navarra, Spain), discussed the development of PEGylated nanoparticles to deliver camptothecin for the treatment of liver cancer.

The talks featured world-leading, highly stimulating science and prompted a number of questions from the audience both during and after each of the sessions. ■

CRS Board Discusses Strategy

The CRS Board met November 7–8, 2014, in San Diego, CA, U.S.A., to discuss strategy to ensure CRS remains the premier society dedicated to delivery science and technology. CRS is a year-round organization, but our signature event is the annual meeting. A large portion of the agenda focused on the annual meeting. Justin Hanes, 2015 Annual Meeting Program Committee chair, joined the Board meeting to discuss proposed changes to the 2015 annual meeting, including the new 10 core areas that will be used to build the scientific sessions, new scientific session format, increased industry involvement, and added novel networking events. The Board also discussed how to increase the value of CRS satellite meetings, reviewed budgets for 2015, and talked about strategies for optimizing industry participation throughout the organization. Members wishing to interact with Board members can find contact information in the member directory or can simply e-mail crspresident@scisoc.org. ■

Left to right: Jamie Oxley, Ruth Schmid, Art Tipton, Debra Bingham, Christopher McDaniel, Maria José Alonso, Ben Boyd, and Ian Tucker

2014 Membership Application

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1061

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People in the News

Compiled by Steven Giannos, Independent Consultant

Zynerba Pharmaceuticals Appoints New Leadership Team: Armando Anido Named Chairman and CEO, Terri Sebree Named President

PRNewswire: October 1, 2014 – RADNOR, PA, U.S.A. – Zynerba Pharmaceuticals, Inc., a specialty pharmaceutical company dedicated to the development of innovative transdermal cannabinoid treatments, today named two leading industry veterans with track records of success in patch and gel transdermal delivery to lead the company. Armando Anido will serve as chairman of the board and chief executive officer, and Terri Sebree will serve as president. Mr. Anido and Ms. Sebree will lead the first and only transdermal cannabinoid therapeutic company as it prepares to initiate phase 1 clinical studies in 2015 on ZYN001, a proprietary prodrug of THC transdermal patch, and ZYN002, a proprietary cannabidiol (CBD) transdermal gel.

Mr. Anido has more than 30 years of executive, operational, and commercial leadership experience in the biopharmaceutical industry. Prior to Zynerba, Mr. Anido served as chief executive officer of two publicly traded companies. Most recently, he was the chief executive officer of NuPathe, which was acquired by Teva Pharmaceuticals in February 2014. At NuPathe, he led the company through FDA approval of its lead product, Zecuity®, the first transdermal patch for migraine, to pre-launch before successfully selling the company to Teva. He also served as president and CEO of Auxilium Pharmaceuticals, where under his leadership, sales grew from $42 million in 2005 to more than $260 million in 2011, driven by the rapid growth of Testim® gel, and market capitalization increased from $200 million to more than $900 million.

Ms. Sebree offers more than 30 years of executive, development, and operational experience in the biopharmaceutical industry, particularly in CNS product development including epilepsy, pain, depression, and schizophrenia. She has completed more than 10 regulatory submissions and approvals of new pharmaceutical products, including transdermal patch and gel products. Prior to Zynerba, Ms. Sebree cofounded and served as president of NuPathe, where she successfully led the effort to develop, achieve regulatory approval, and complete manufacturing of the company's lead product, Zecuity. Previously, Ms. Sebree served as senior vice president, development, of Auxilium Pharmaceuticals, where she led the Testim gel development and approval program.

"Armando and Terri both have demonstrated the ability to rapidly grow pharmaceutical companies and are uniquely experienced in leading the development, regulatory approval, and commercialization of both patch and gel transdermal pharmaceuticals," said Philip Wagenheim, former chairman and current board member of Zynerba. "We are confident that these high-caliber leaders will strategically guide the company as it enters clinical development of these novel transdermal candidates in the coming months."

"As the first and only transdermal cannabinoid company, Zynerba is well positioned as it develops two highly innovative therapeutic treatments for the millions of patients who suffer from chronic and debilitating diseases such as fibromyalgia, neuropathic pain, chronic cancer pain, epilepsy, and rheumatoid arthritis," said Armando Anido, chairman and CEO of Zynerba Pharmaceuticals. "These novel synthetically produced candidates may offer unique advantages by delivering drug through the skin and into the bloodstream. Terri and I believe that these proprietary treatments, combined with a large population of underserved patients, offer significant promise, and we look forward to advancing our pipeline." ■

In the News

Compiled by Steven Giannos, Independent Consultant

October

Nanotechnology Venture Targets Arterial, Heart ,and Kidney Diseases

PRNewswire: October 16, 2014 – ASHLAND, MA, U.S.A. – NuVascular Technologies, Inc., is commercializing its patented electrospinning process to create new medical devices that help millions.

Recently spun out from Biosurfaces, Inc., the company uses cutting-edge nanotechnology that would target serious conditions such as arterial, heart, and kidney diseases.

The platform technology was developed over a 10-year period as a result of $6.6 million in funding obtained from National Institutes of Health. The newly formed NuVascular Technologies, currently in discussions with the FDA, holds an exclusive license for this technology and has a management team with a wealth of experience in the health, research, and academic fields.

Cofounders Eugene J. Anton, a serial entrepreneur with a history of success in the biotechnology space, and Matthew D. Phaneuf, an established biomaterials scientist with a track record of award-winning research and an inventor of the technology, are developing medical solutions that mimic the natural scaffold onto which tissue grows while also incorporating targeted drug delivery. Using the latest in nanotechnology, NuVascular Technologies' groundbreaking electrospinning process will help treat different aspects of arterial, heart, and kidney diseases with the goal of dramatically reducing complications.

"These diseases affect millions in the United States and around the world. We've seen the heartbreaking impact that heart, vascular, and kidney diseases have on the patients and their families," Anton said.

Approximately 200 million people worldwide are affected by arterial disease. In the United States, 26 million people are at risk for end-stage renal disease, and 5.1 million are affected by heart failure.

"The numbers are staggering. With so many people afflicted with these diseases, there needs to be better options available," Phaneuf said. "The progress made at NuVascular Technologies will help to reduce complications associated with these devices and speed up the healing process, allowing these people to return to a better quality of life."

The NuVascular Technologies' approach is a vast improvement over the current industry standard of thicker woven and knitted biomaterials, which never fully heal within the body, resulting in possible complications. With NuVascular Technologies' devices, drugs and other bioactives are incorporated directly into the electrospun fibers, drastically improving healing and reducing complications. This "first-in-class" drug loading allows for a release rate and duration that can be tailored for specific devices and is a vast improvement to mainstream approaches, which either do not have the capacity to locally deliver drugs or use binding agents that can cause complications. These technologies far exceed the benefits of other treatments in the market.

Zynerba Pharmaceuticals Raises $13 Million to Develop First and Only Transdermal Cannabinoid Therapies

PRNewswire: October 15, 2014 – RADNOR, PA, U.S.A. – Zynerba Pharmaceuticals, Inc., a specialty pharmaceutical company dedicated to the development of innovative transdermal cannabinoid treatments, today announced the successful closing of $13 million in funding. New investors in Zynerba include one of the top seven life sciences public investors, Perceptive Advisors LLC. Proceeds of the fundraising will be used for development efforts for the first and only transdermal cannabinoid therapies as Zynerba prepares to initiate phase 1 clinical studies in 2015 on ZYN001, a proprietary prodrug of THC transdermal patch, and on ZYN002, a proprietary cannabidiol (CBD) transdermal gel.

"We thank our new investors for their confidence in Zynerba as the first and only transdermal cannabinoid company," said Armando Anido, chairman and CEO of Zynerba Pharmaceuticals. "This funding allows us to advance our two highly innovative and proprietary cannabinoid therapeutic development assets for large unmet patient populations. We believe these novel, synthetically produced candidates may offer unique advantages by delivering drug through the skin and into the bloodstream, presenting significant promise to patients."

Zynerba Pharmaceuticals is dedicated to the development of innovative transdermal cannabinoid treatments for patients with high unmet medical needs using modern drug delivery technology and appropriate regulatory pathways. Zynerba is developing two therapeutic candidates based on proprietary transdermal technologies that, if successfully developed, may allow sustained, consistent, and controlled delivery of therapeutic levels of cannabinoids. Transdermal delivery reduces adverse effects associated with oral dosing. ZYN001 will be studied in fibromyalgia, neuropathic pain, and chronic cancer pain utilizing a synthetically manufactured prodrug of THC in a transdermal patch to deliver THC through the skin and into the bloodstream. Zynerba expects to initiate ZYN001 phase 1 clinical studies in 2Q 2015. ZYN002 will be studied in epilepsy and rheumatoid arthritis, utilizing a proprietary gel to deliver synthetically manufactured cannabidiol (CBD), a nonpsychotropic cannabinoid, through the skin and into the

bloodstream. Zynerba expects to initiate ZYN002 phase 1 clinical studies in 3Q 2015. Learn more at www.zynerba.com and follow the company on Twitter at @ZynerbaPharma.

Ocular Therapeutix™ Completes Enrollment in Phase 3 Sustained Release Dexamethasone Trials for Postoperative Inflammation and Pain

Business Wire: October 8, 2014 – BEDFORD, MA, U.S.A. – Ocular Therapeutix, Inc. (NASDAQ: OCUL) announced today completion of enrollment for its two phase 3 clinical trials evaluating sustained release dexamethasone (OTX-DP) for treatment of ocular inflammation and pain following cataract surgery. OTX-DP is a one-time administration product candidate placed in the canaliculus and designed to deliver dexamethasone to the ocular surface for approximately four weeks. Following treatment, OTX-DP resorbs and exits the nasolacrimal system without the need for removal.

The two prospective, multicenter, randomized, parallel-arm, double-masked, vehicle-controlled studies are evaluating 486 patients at 32 sites throughout the United States. Following surgery, patients were randomized to receive either OTX-DP or a placebo vehicle punctum plug without active drug. Primary efficacy endpoints for the studies are the absence of inflammatory cells in the anterior chamber of the eye at day 14, and reduction of pain at day 8.

"Completion of enrollment for OTX-DP is an extraordinary milestone for our company, not only as our first phase 3 clinical trials for a sustained release pharmaceutical, but also the first phase 3 trials ever to be completed for a sustained release, drug delivery punctum plug," stated Amar Sawhney, Ph.D., president and CEO of Ocular Therapeutix, Inc. "We look forward to submitting results to the FDA in 2015."

Topical corticosteroids are typically prescribed to treat ocular inflammation and pain following ophthalmic surgery. However, topical steroid regimens can be complex, which can lead to lower levels of compliance and thus may adversely affect outcomes. Conversely, chronic administration of topical corticosteroids can lead to spikes in intraocular pressure, which may induce glaucoma. A physician administered, single-dose corticosteroid puts compliance in the hands of physicians, and may improve issues of patient noncompliance with dosing regimens.

"OTX-DP is easily inserted and can be monitored by the physician during the postoperative period," stated Thomas R. Walters, M.D., principal investigator at Texan Eye in Austin, Texas. "In a previously completed phase 2 clinical trial, treatment with OTX-DP significantly relieved pain at day 8, as reported by the patient, and inflammation at day 14, as measured by absence of inflammatory cells in the anterior chamber of the eye, compared to vehicle control, and patients were comfortable with the plug."

Sustained release dexamethasone (OTX-DP) is a drug product candidate that is placed within the canaliculus and delivers the corticosteroid dexamethasone to the ocular surface for approximately four weeks. The drug release is tailored such that a low dose is sustained throughout the treatment period, and it incorporates a natural taper to mimic a topical postoperative regimen.

Ocular Therapeutix, Inc., is a biopharmaceutical company focused on the development and commercialization of innovative therapies for diseases and conditions of the eye using its proprietary hydrogel platform technology. Ocular Therapeutix's lead product candidates are in phase 3 clinical development for postsurgical ocular inflammation and pain and phase 2 clinical development for glaucoma and allergic conjunctivitis. The company is also evaluating sustained-release injectable anti-VEGF drug depots for back-of-the-eye diseases. Ocular Therapeutix's first product, ReSure® Sealant, is FDA-approved to seal corneal incisions following cataract surgery.

Neos Therapeutics Announces Issuance of Key Patent Covering Its Extended Release Oral Disintegrating Tablet (XR-ODT) Platform Technology

Business Wire: October 8, 2014 – DALLAS and FORT WORTH, TX, U.S.A. – Neos Therapeutics, Inc. ("Neos"), a specialty pharmaceutical company with a portfolio of novel and proprietary oral drug delivery technologies as well as a late-stage pipeline of innovative extended release ("XR") products for attention deficit hyperactivity disorder ("ADHD"), announced today that is has been granted a key patent (U.S. patent no. 8,840,924) covering its XR-oral disintegrating tablet ("ODT") technology, known as Rapidly Disintegrating Ionic Masking™ (RDIM™).

RDIM™ utilizes an orally disintegrating, controlled release, taste-masked pharmaceutical composition that can withstand compression forces associated with standard tableting technology, allowing for a drug to be incorporated into the ODT dosage form using ion resin technology. This technology not only provides extended release or controlled release properties, it can also mask the unpleasant taste of the drugs.

ODTs are tablets that disintegrate quickly when placed on the tongue and thus facilitate ingestion of a tablet. By combining the ODT dosage form with controlled release properties, Neos' XR-ODT formulations can benefit those patients who have difficulty swallowing intact tablets and capsules and who require extended release products. XR-ODTs are easily transported, can be taken without liquid, and provide convenient and easy to administer dosage form for patients and caregivers.

"This XR-ODT technology is embedded in two near-term products that Neos is developing. NT-0102 is an XR-ODT of methylphenidate, and NT-0202 is an XR-ODT of amphetamine. Methylphenidate and amphetamine are two of the most prescribed compounds for the treatment of ADHD. The application of XR-ODT technology to ADHD was obvious, as the medications for ADHD need to be administered effectively and last all day long," stated Vipin K. Garg, Ph.D., president and CEO of Neos.

In the News continued on page 30

In the News continued from page 29

"This patent further strengthens Neos' intellectual property position and further protects our proprietary product candidates," said Mark Tengler, chief technology officer of Neos. "We believe that our XR-ODT technology will have a broad applicability in multiple therapeutic areas."

Neos Therapeutics, Inc., is a fully integrated specialty pharmaceutical company. The company is initially focusing on ADHD with three proprietary products in late-stage development that provide patient-friendly dosage forms incorporating controlled and extended release oral disintegrating tablets (ODT) and liquid suspensions. In addition, Neos manufactures and markets a generic of Tussionex®, for the treatment of cough and cold. The company's products are developed and manufactured using its proprietary and patented ion resin technology. For more information, visit www.neostx.com.

Icon Bioscience Reports Last Patient Out in Its Phase 3 Study of IBI-10090 as a Dropless, Sustained-Released Therapeutic for Inflammation Associated with Cataract Surgery

Business Wire: October 6, 2014 – SUNNYVALE, CA, U.S.A.– Icon Bioscience, Inc., a specialty biopharmaceutical company focused on utilizing its Verisome® drug-delivery platform to develop unique intraocular eye-care therapeutics, today announced that the last patient has completed treatment in its pivotal phase 3 study of IBI-10090. Top-line data is expected to be reported in the fourth quarter of 2014.

Employing Icon's Verisome technology, IBI-10090 is designed to provide a controlled, sustained-release formulation of the anti-inflammatory agent dexamethasone into the anterior chamber of the eye through a single injection administered immediately following cataract surgery.

Over three million cataract surgeries are performed annually in the United States alone, and the current standard of care for inflammation associated with the surgery involves a comparatively burdensome process of patient-administered eye drops applied topically several times a day over an extended time period. "Thus, the superior drug delivery benefit of IBI-10090 addresses a significant product opportunity in a fairly large ophthalmic pharmaceutical space," said David S. Tierney, M.D., Icon's president and CEO.

The phase 3 study of IBI-10090 involved 390 patients in a randomized, double blind, and placebo-controlled study. "A previous phase 2 study, demonstrated a highly favorable efficacy and safety profile, and we eagerly await results of the completed phase 3 study," noted Tierney.

Nitto: New Anti-Fibrosis Drug with Molecular Targeting DDS Starts Phase-1B Dosing for Cirrhosis Patients

Business Wire: October 6, 2014 – OSAKA, Japan – Nitto Denko Corporation (Nitto) (TOKYO: 6988) (ISIN: JP3684000007) announces the initiation of a phase-1b clinical study in the United States started in September 2014 to administer a new anti-fibrosis drug in patients for the assessment of safety and efficacy.

Nitto has been developing an RNAi based drug for treating fibrosis in the liver and other organs since 2008 in collaboration with Sapporo Medical University and Hokkaido University. In March 2014, a phase-1 clinical study in healthy volunteers was completed, and no remarkable adverse events were observed, even at the highest dose tested. After thorough analysis of the data, the study results were summarized in a clinical study report, which concluded that the drug was safe and well tolerated. These results served as the basis of the phase-1b clinical study plan.

The clinical study plan has been approved by a central institutional review board (IRB). This allows Nitto to initiate the phase-1b clinical study in subjects with moderate to severe liver fibrosis for the assessment of safety and efficacy of the drug. Following the start of the U.S. study, Nitto will also conduct a clinical study in Japan.

The clinical studies in the United States have been conducted in collaboration with RRD International, Inc. (Rockville, MD), a product development company that provides expert-level strategic, regulatory, and operational support.

Discovery Labs Receives SBIR Grant Valued up to $3.0 Million to Support Development of Aerosolized KL4 Surfactant to Address Radiation-Induced Lung Injury

PRNewswire: October 1, 2014 – WARRINGTON, PA, U.S.A. – Discovery Laboratories, Inc. (Nasdaq: DSCO) today announced that the company has been awarded a phase II Small Business Innovation Research Grant (SBIR) valued at up to $3.0 million from the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) to support the development of the company's aerosolized KL4 surfactant as a medical countermeasure to mitigate acute and chronic/late-phase radiation-induced lung injury. The company has been awarded $1.0 million and over the next three years may be awarded up to an additional $2.0 million as part of this grant. This program will be conducted in conjunction with Melpo Christofidou-Solomidou, Ph.D., a leading expert in novel antioxidant approaches to acute and chronic lung diseases from the University of Pennsylvania's Perelman School of Medicine. In fiscal year 2010, the Perelman School of Medicine received $583 million in support for its research activities from extramural sponsors, including $408 million from the National Institutes of Health, ranking third in the nation among all academic medical institutions.

"While we remain focused on respiratory distress syndrome in premature infants, we believe that our proprietary KL4 surfactant also has the potential to address a number of other lung diseases and complications, including certain acute lung injuries," commented John G. Cooper, Discovery Lab's president and chief executive officer. "The NIH has previously provided Discovery

Labs funding to assess these potential opportunities and, based on the encouraging results of that preliminary work, has provided additional funding to continue research in this area. Radiation-induced pulmonary injury is a common and complicated manifestation of radiation exposure, and we look forward to developing data that may help define the role of KL4 surfactant in protecting irradiated lungs."

The company believes that its proprietary KL4 surfactant may have utility in a variety of radiation-induced lung injuries, a common term referencing not only damage to the lungs occurring as a result of a radiological accident or terrorism threat agent but also lung damage occurring as a result of radiation therapy as a treatment modality for a number of thoracic malignancies. Studies have suggested that radiation-induced pneumonitis may occur in up to 15% of patients receiving radiation therapy for lung cancer.

KL4 surfactant is a novel synthetic, peptide-containing surfactant designed to closely mimic the essential attributes of human lung surfactant. Discovery Labs is currently evaluating aerosolized KL4 surfactant in an ongoing phase 2a clinical program to assess safety and tolerability of aerosolized KL4 surfactant delivered to premature infants receiving nasal continuous positive airway pressure (nCPAP) for respiratory distress syndrome (RDS).

Government support and interest in Discovery Labs' aerosolized KL4 surfactant program stems from the passing of the Project Bioshield Act of 2004 and the Pandemic & All-Hazards Preparedness Act of 2006 by the U.S. Congress. Both acts encourage private-sector development of medical countermeasures against chemical, biological, radiological, and nuclear terrorism threat agents and pandemic influenza, and provide a mechanism for federal acquisition of such countermeasures.

September

pSivida Corp. Reports FDA Approval of ILUVIEN® for Diabetic Macular Edema

Business Wire: September 26, 2014 – WATERTOWN, MA, U.S.A. – pSivida Corp. (NASDAQ: PSDV, ASX: PVA), a leader in the development of sustained release drug delivery products for treating eye diseases, today announced that the U.S. Food and Drug Administration (FDA) has approved ILUVIEN® for the treatment of diabetic macular edema (DME). It is indicated for patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure (IOP). A single injection of the ILUVIEN microinsert provides sustained treatment of DME for 36 months. Approximately 560,000 people in the United States are estimated to have clinically significant DME, the most frequent cause of vision loss in individuals with diabetes and the leading cause of blindness in young and middle-aged adults in developed countries. ILUVIEN is expected to be commercially available in the United States in early 2015.

FDA approval of ILUVIEN entitles pSivida to a $25 million milestone from its licensee Alimera Sciences. pSivida will also be entitled to 20% of the net profits from sales of ILUVIEN in the United States.

"FDA approval of ILUVIEN, our third FDA-approved product for retinal disease, provides an important treatment option for DME patients in the United States, the majority of whose DME, despite anti-VEGF intraocular injections as frequently as monthly, is not optimally managed. ILUVIEN's clinical trials showed that ILUVIEN can actually reverse vision loss in many DME patients. Another advantage of ILUVIEN over existing therapies is that a single injection provides sustained therapy for three years," said Paul Ashton, Ph.D., president and chief executive officer of pSivida.

"The $25 million milestone will help finance our ongoing product development program, including Medidur™ for posterior uveitis and Tethadur™ for the sustained delivery of biologics," added Dr. Ashton. pSivida is independently developing Medidur, an injectable sustained-release microinsert of the same design and delivering the same drug as ILUVIEN, for the treatment of chronic posterior uveitis, the third largest cause of blindness in the United States. The company plans to seek FDA approval of this product on the basis of its ongoing single phase III clinical trial. Enrollment of this study is expected to be completed by the end of the first quarter of calendar 2015.

ILUVIEN is already commercially available in the United Kingdom and Germany and has received or is pending marketing approval in 17 other EU countries for the treatment of patients with chronic DME insufficiently responsive to available therapies. "We are very pleased that the FDA's approval of ILUVIEN is not limited, as in the EU, to the subset of patients with chronic DME, patients who have failed other therapies, or patients who have had cataract surgery," continued Dr. Ashton.

ILUVIEN is an injectable microinsert that provides sustained treatment through continuous delivery of a submicrogram dose of the corticosteroid fluocinolone acetonide for 36 months. Current standard-of-care therapy requires anti-VEGF injections into the eye as frequently as monthly, and studies show that over 50% of patients are not optimally managed with this treatment. FDA approval was based on clinical trial data that showed that at month 24, 28.7% of patients receiving ILUVIEN experienced an improvement from baseline in their best corrected visual acuity on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart of 15 letters or more. This improvement in vision was maintained through 36 months, the end of the trials.

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is a sustained-release intravitreal implant approved in the United States to treat DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. Each

In the News continued on page 32

In the News continued from page 31

ILUVIEN implant is designed to release submicrogram levels of fluocinolone acetonide (FAc), a corticosteroid, for 36 months.

Corticosteroids have a history of effective use in treating ocular disease inflammation. ILUVIEN is injected in the back of the patient's eye with an applicator that employs a 25-gauge needle, which allows for a self-sealing wound. In the FAME™ study, a phase 3 clinical study of ILUVIEN, the most frequently reported adverse drug reactions included cataract development and increased ocular pressure.

Noven Receives FDA Approval of a New Indication with a New Dose for Minivelle® (Estradiol Transdermal System)

PRNewswire: September 24, 2014 – MIAMI, FL and NEW YORK, NY, U.S.A. – Noven Pharmaceuticals, Inc., announced today that the U.S. Food and Drug Administration (FDA) has approved a new indication with a new dose of Minivelle (estradiol transdermal system) for the prevention of postmenopausal osteoporosis. The FDA initially approved Minivelle in October 2012 to treat moderate to severe vasomotor symptoms (VMS) due to menopause, commonly known as hot flashes. With this new approval, women who are using Minivelle to treat their VMS symptoms have the benefit of also helping to prevent osteoporosis.

The new 0.025 mg/day patch is 33% smaller than Minivelle 0.0375 mg/day that is already only about the size of a dime, the planet's smallest estrogen therapy patch ever. Minivelle is now approved with five dosing options: 0.025, 0.0375, 0.05, 0.075, and 0.1 mg/day, with the newly approved lower dose of 0.025 mg/day indicated for the prevention of postmenopausal osteoporosis only. If a patient uses Minivelle only to prevent osteoporosis from menopause, they should talk with their healthcare provider about whether a different treatment or medicine without estrogens might be better for them.

"Noven is deeply committed to offering therapies that address women's menopausal health," said Joel Lippman, M.D., FACOG, Noven's executive vice president – product development and chief medical officer. "We're pleased that we now have an additional indication and the new dosage strength available for Minivelle to allow women and their doctors to individualize their treatment to best fit their needs."

The new lower dose of 0.025 mg/day is expected to be available in pharmacies in January 2015. Noven offers a savings program to help reduce the Minivelle copay for eligible patients. Eligible patients pay no more than $15 each month for up to 12 uses on their Minivelle prescriptions. Restrictions may apply. For more information, including full terms and conditions, visit www.minivelle.com.

Novaliq GmbH Reports Positive Results from CyclASol® (Cyclosporin Solution) Eye Drops Repeated and Ascending Dose Phase 1 Study

Business Wire: September 23, 2014 – HEIDELBERG, Germany – Novaliq GmbH, a drug delivery company with focus on the topical application of ophthalmic technologies for poorly soluble drugs, today reported positive phase 1 results with the first and only clear cyclosporin solution eye drop formulation in clinical development for patients with dry eye syndrome.

Objectives of the 18 patient phase 1, double-blind, randomized, placebo-controlled cross-over study were to investigate safety, local tolerability, and systemic exposure of CyclASol® (cyclosporin solution) eye drops and vehicle following single and multiple ocular doses in healthy volunteers.

No drug-related signs or symptoms of ocular discomfort or irritation were reported, in particular no dryness, grittiness, burning, stinging, tiredness, blurred or foggy vision, redness, watery eyes, eye mucus, or crusting. In slit-lamp examinations, no subjects revealed any clinically abnormal signs of the anterior and posterior eye structures. With dosing of up to four drops per eye per day, no systemic levels of cyclosporin were detected after any dose or at any time point when using a highly sensitive assay with a LLOQ as low as 0.1 ng/mL.

"For patients with dry eye disease, there are few approved drug options available. Cyclosporin is a well-accepted active drug substance for this disease, although current formulations come with several limitations including side effects and limited patient acceptance due to cyclosporin's poor solubility," said Novaliq's chief scientific officer Dieter Scherer, Ph.D.

"We are very pleased by the study results, since they clearly show that our innovative clear solution formulation of cyclosporin using our EyeSol® platform technology is safe and convenient for patients. We have a granted patent position in most relevant markets and look forward to continuing our clinical development trials in dry eye disease either on our own or with interested partners," added Bernhard Guenther, president and CEO, Novaliq.

"We congratulate Novaliq on their proprietary EyeSol® platform technology, as it continues to deliver on the promise as an innovative safe and well-tolerated ophthalmic delivery technology. After NovaTears® OTC, CyclASol® is the second Novaliq product with positive data in humans," said Mathias Hothum from Novaliq's main investor, dievini Hopp BioTech holding GmbH and Co KG.

Telormedix Granted European Patent for Vesimune

Business Wire: September 22, 2014 – BIOGGIO, Switzerland – Telormedix, a clinical stage biopharmaceutical company focused on TLR7 agonists in the treatment of cancer and infectious diseases, announced today that it has been granted European patent no. 2393474 entitled "Pharmaceutical compositions comprising imidazoquinolin (amines) and derivatives thereof suitable for local administration" by the European Patent Office. The European patent, which will expire in 2030, broadly covers Telormedix's lead product, Vesimune (TMX-101), and its use for the treatment of bladder cancer. Further patents for Telormedix's Vesimune have also recently been granted in China and Australia.

Vesimune is Telormedix's lead product, a TLR-7 agonist that currently has successfully completed a phase II trial in CIS (carcinoma *in situ*) of the bladder. The product is a unique sterile liquid formulation of a marketed immune modulatory compound, designed on innovative technology principles to carrier drug delivery systems in order to increase solubility, bioadhesiveness, and stability. These properties mean that the product can be used in therapeutic settings that the original product could not.

Dr. Johanna Holldack, CEO of Telormedix, commented: "This patent is the single most important patent for Vesimune, our lead compound for the treatment of bladder cancer. With our recent positive phase II results, this patent puts us in a strong position for partnering discussions."

Telormedix's lead product, Vesimune (TMX-101), is a targeted small molecule for the treatment of superficial bladder cancer. The active ingredient in Vesimune is a known immunomodulatory molecule with a favorable safety profile and a demonstrated clinical efficacy in oncological and viral diseases. The company expects that this targeted therapy will have an improved safety and efficacy profile in comparison to standard of care. Telormedix has taken advantage of existing regulatory data and clinical experience in order to bring Vesimune quickly through phase I/II clinical trials.

Telormedix (www.telormedix.com), founded in October 2007, is a biopharmaceutical company focused on targeted immunity and modulation of the innate immune system for treating cancer and infectious diseases. The company's lead product, Vesimune (TMX-101), has just successfully completed a phase II clinical trial for the treatment of CIS (carcinoma *in situ*) of the bladder. In addition, Telormedix is developing two additional TLR7-targeted molecules, TMX-201 and TMX-202, both of which would make good vaccine adjuvants. As these molecules have substantially improved pharmacokinetics and pharmacodynamics profiles, they have the potential to fully realise the anticancer promise of TLR 7 agonists. One of these molecules, TMX-202, has recently been selected for preclinical study for the topical treatment of skin cancers and other indications. The candidate has already successfully completed a number of *in vivo* studies.

Located in Switzerland, Telormedix is led by a highly experienced management team and backed by an international consortium of venture capitalists, Aravis (Zurich, Switzerland) and Proquest Investments (Florida, U.S.A.).

Moberg Pharma Announces Successful Results for MOB-015 in a Phase II Study for the Treatment of Onychomycosis

Business Wire: September 17, 2014 – STOCKHOLM, Sweden – Moberg Pharma AB (OMX: MOB) announces successful top-line results from a phase II study for MOB-015 in onychomycosis (nail fungus). The primary endpoint, mycological cure after 15 months, was achieved in 54% of the patients.

The purpose of the study was to demonstrate proof-of-concept for MOB-015 in onychomycosis. The open-label clinical study including 25 patients was conducted at Sahlgrenska University Hospital, Sweden, with Prof. Jan Faergemann as the coordinating investigator. Patients with onychomycosis affecting 25–75% of at least one great toe nail received treatment with MOB-015 during 12 months and were followed for a total of 15 months. The study included patients with more severe onychomycosis than recently published studies of topical treatment alternatives. Of the 24 patients who completed the study, 13 (54%) met the primary endpoint, mycological cure, defined as both negative microscopy and fungal culture after 15 months from start of treatment. The secondary endpoint, mycological cure and excellent clinical improvement or cure, was observed in 7 of 24 patients (29%). Biopsies confirmed high levels of terbinafine in the nail plate and nail bed (median values 1,610 and 45 µg/g, respectively). MOB015 was generally well tolerated.

"The mycological cure rate and clinical outcome in the study are remarkable for a topical treatment. Especially since the majority of these patients had more than 50% nail involvement at inclusion. These results are promising for future phase III studies. An efficacious and safe topical terbinafine product would be highly attractive for dermatologists worldwide," stated Dr. Jan Faergemann, M.D., Ph.D., Professor, Dermatology Unit at Sahlgrenska University Hospital.

"The excellent phase II results exceeded our expectations. MOB-015 has the potential to become a superior and leading product in the large and growing onychomycosis market. We are now proceeding with partner discussions for further development and commercialization of MOB-015," said Peter Wolpert, CEO of Moberg Pharma AB.

MOB-015 is a proprietary topical formulation of terbinafine developed by Moberg Pharma. Terbinafine is currently the most widely used oral prescription treatment for onychomycosis and was a blockbuster before patent expiry. Topical administration of terbinafine eliminates concerns of oral treatment, such as drug interactions or liver injury, but has previously not been successful due to insufficient delivery of the active substance through the nail. Preclinical and clinical data confirm that MOB-015 delivers effective levels of terbinafine through the nail and into the nail bed.

Onychomycosis is a common nail infection caused predominantly by dermatophyte fungi that typically occurs under the toenail, although fingernails may also be affected. Approximately 10% of the general population suffers from onychomycosis. The estimated market potential exceeds USD 1 billion in the United States only. The untapped potential is significant since the majority of patients are untreated.

Moberg Pharma AB (publ) is a rapidly growing Swedish pharmaceutical company with a direct sales and marketing organization in the United States and an extensive distributor

In the News continued on page 34

In the News continued from page 33

network in more than 40 countries. The company's OTC portfolio includes the brands Kerasal®, Jointflex®, Kerasal Nail®, Domeboro®, Vanquish®, and Fergon®. Kerasal Nail® (Nalox™ in certain ex-U.S. markets) is the leading product for the treatment of nail disorders in the U.S. and Nordic market. The current portfolio will be supplemented by the acquisition and in-licensing of additional products as well as product development with a focus on innovative drug delivery of proven compounds. Moberg Pharma has offices in Stockholm and New Jersey, and the company's shares (OMX: MOB) are listed on the Small Cap list of the NASDAQ OMX Nordic Exchange Stockholm. For further information, please visit www.mobergpharma.com.

Genisphere Closes $2 Million to Accelerate Development of Targeted Drug Delivery Platform

Business Wire: September 16, 2014 – HATFIELD, PA, U.S.A. – Genisphere LLC, provider of the 3DNA® nanotechnology platform, reported today it has closed $2 million in private funding from existing investors, including Corporate Fuel Partners, a New York fund. This round of fundraising will accelerate Genisphere's targeted drug delivery initiative, following key milestones including the company's demonstration of cell-specific (cytosolic and nuclear) delivery of drugs with functional intracellular effects without apparent toxicity.

"3DNA nanotechnology is a versatile and unique delivery platform with potentially diverse and enormously important medical applications," noted Vladimir Muzykantov, M.D., Ph.D., director of the Center for Targeted Therapeutics and Translational Nanomedicine (CT3N) at the University of Pennsylvania.

"Genisphere has created an impressive portfolio of joint projects to identify the most promising leads and expand the evolving practical applications beyond the initial prototypes," he added. "Genisphere's corporate membership in CT3N offers it direct access to leading experts in the field; indeed, University of Pennsylvania counterparts have been intrigued by delivery opportunities provided by 3DNA technology."

Genisphere established these key collaborations to generate preclinical data showing the versatility and efficacy of the 3DNA platform in targeted delivery of small drugs, biologics, and nucleic acids. Last year, Genisphere announced its first research collaboration agreement with MultiCell Technologies, Inc. (OTC: MCET), which is investigating the use of the 3DNA platform to help facilitate the targeted delivery of their lead drug candidate, MCT485, for the treatment of primary hepatocellular carcinoma. The number of collaborations has now grown to more than 25 and includes several projects with large pharmaceutical companies.

"Pre-clinical data have demonstrated specific targeting of tumors, selective killing of targeted cells, tumor shrinkage, and no observed toxicity," said Bob Getts, Genisphere's chief science officer. According to Getts, key milestones achieved included excellent biodistribution profiles, transport across the blood-brain barrier, and specific accumulation in targeted tumors.

Getts also pointed out the flexibility of the 3DNA platform to deliver hundreds of tracking labels to targeted tissues, providing pharma companies with an option to incorporate a companion diagnostic into the drug development process. He summarized, "This round of funding will accelerate our joint efforts with our current collaborators, and gives Genisphere the resources to support additional partnerships."

Genisphere also plans to advance its own lead oncology compounds based on the 3DNA drug delivery platform.

Genisphere LLC is a targeted drug delivery platform company. Genisphere's platform is a DNA-based nanotechnology called 3DNA®. 3DNA nanocarriers are used to deliver drugs in a highly targeted manner. Genisphere's technology is IP-protected and fully customizable to deliver a variety of therapeutics including small drugs, biologics, and nucleic acids. 3DNA nanostructures are composed entirely of DNA, engineered and cross-linked to form a stable architecture while maintaining the biocompatibility of the nucleic acid building blocks. Genisphere has been leveraging a collaborative model to advance its drug delivery platform and continues to seek partnerships with biotechnology and pharmaceutical companies that could benefit from the company's platform technology. Genisphere is also advancing its own lead compounds based on the 3DNA platform. For more information, please visit http://genisphere.com.

Micell Technologies Highlights Positive Three-Year Data from MiStent SES DESSOLVE Clinical Studies at TCT 2014

PRNewswire: September 16, 2014 – DURHAM, NC, U.S.A. – Micell Technologies, Inc., today announced that three-year clinical results from the DESSOLVE I and DESSOLVE II trials of its MiStent sirolimus eluting absorbable polymer coronary stent system (MiStent SES®) were presented at the 26th Annual Transcatheter Cardiovascular Therapeutics (TCT) Conference being held in Washington, D.C., September 13–17. MiStent SES is designed to optimize vessel healing in patients with coronary artery disease, and these data demonstrated desirable bare-metal stent type healing. Normal endothelial function was maintained, and there was minimal progression of late lumen loss through 18 months' follow-up. In addition, the DESSOLVE studies had an overall target lesion revascularization (TLR) rate of 2.0% with no probable or definite stent thromboses related to MiStent SES at three years' follow-up.

"Three Year Clinical Outcomes of a Unique Sirolimus-Eluting Stent with Fully Absorbable Polymer Coating: Long-Term Results from the DESSOLVE I and the DESSOLVE II Clinical Trials" was presented in poster and oral formats as part of the Didactic Symposia, "Metallic DES: Tomorrow's Technology." John Ormiston, M.B.Ch.B., interventional cardiologist with the Mercy Angiography Unit, Auckland, New Zealand, presented the data. Dr. Ormiston is a principal investigator in the DESSOLVE studies.

Dr. Ormiston commented, "The MiStent SES is the sole product among the new generation of bioabsorbable polymer DES to sustain local drug delivery beyond the presence of the polymer, providing therapeutic sirolimus drug levels in the tissue surrounding the stent for up to nine months. Full elimination of the polymer by three months—without loss of anti-restenotic drug effects—is different from any other DES formulation."

Dennis Donohoe, M.D., Micell's chief medical advisor, added, "MiStent SES provides a unique bioabsorbable DES stent design profile with consistent long-term data. We are excited to see that the safety profile of this stent has remained consistent over three years with no probable or definite stent thromboses related to its use."

to-BBB Announces Positive Data from Phase 1 Clinical Study

Business Wire: September 12, 2014 – LEIDEN, Netherlands – to-BBB, a biopharmaceutical company focusing on treatments for devastating brain diseases, today announced positive clinical data for its product candidate designed to treat neuroinflammation, 2B3-201, from an ongoing phase 1 clinical trial in healthy volunteers and MS patients. The study was conducted in collaboration with the Center for Human Drug Research (CHDR), Leiden, the Netherlands. The results, presented Thursday, September 11, at the 2014 Joint ACTRIMS-ECTRIMS (Americas Committee and European Committee for Treatment and Research in Multiple Sclerosis) Meeting in Boston, provide evidence that 2B3-201 is safe and well-tolerated at therapeutic dose levels and has a greatly increased plasma half-life and prolonged effects supporting a single administration.

In the presented double-blind crossover phase 1 clinical trial, a total of 18 healthy male subjects were divided over three cohorts and received ascending doses of 2B3-201 up to 450 mg, active comparator (free methylprednisolone, MP) up to 1,000 mg, or placebo (5% dextrose). The trial reported no serious adverse events (AEs) following single administration of 2B3-201, and all AEs reported were mild and self-limiting. The trial is currently expanded to include 18 additional healthy male and six additional healthy female subjects, as well as 18 MS patients.

"Based on evidence of extended half-life, long-lasting immunosuppressive effects and solid safety data, we are excited to move forward with a study expansion," said Werner Gladdines, head of development at to-BBB. "Our goal is to deliver a safe and convenient therapeutic option with reduced side effects to MS patients."

Dr. Anders Harfstrand, chief executive officer of to-BBB, added: "With these promising clinical results we have made a significant step forward towards proof of concept for both 2B3-201 and our pipeline developed from our G-Technology®."

MS is a chronic disease of the CNS, and relapses are characterized by acute neurological impairment. For these relapse events, standard of care are intravenous injections of high-dose MP at 500–1,000 mg daily for three to five consecutive days. 2B3-201 consists of our proprietary glutathione PEGylated liposomal methylprednisolone (G-Technology®) and is designed to enable improved passage of the drug into the patient's brain through single-dose treatment, reducing both dose and dosing frequency, ideally resulting in reduced side effects but with at least similar efficacy.

to-BBB's proprietary G-Technology® offers a way to safely enhance brain delivery of drugs that do not readily reach the brain within a favorable therapeutic window. G-Technology® is a drug delivery system that can carry a wide range of compounds in small vesicles, so-called liposomes, thereby protecting the body from side effects caused by peak drug concentrations. Two molecules, polyethylene glycol (PEG) and glutathione, are attached to the liposomes to ensure a prolonged circulation time in the blood stream and to improve passage of the drugs across the blood-brain barrier.

to-BBB is developing medicines for the treatment of devastating brain diseases. Our proprietary liposomal G-Technology® facilitates entry to the brain while simultaneously enabling sustained delivery of systemically administered therapeutics. Our technology has been shown to be compatible with approved as well as novel therapeutic entities. We have two clinical programs, one targeting multiple indications of brain cancers and the other neuroinflammatory diseases.

Neos Therapeutics Acquires All Commercialization and Profit Rights to Generic Tussionex® (Extended Release Hydrocodone Polistirex/Chlorpheniramine Polistirex) from Chiesi USA and Coating Place, Inc.

Business Wire: September 8, 2014 – DALLAS and CARY, NC, and VERONA, WI, U.S.A. – Neos Therapeutics, Inc. ("Neos"), a specialty pharmaceutical company with a portfolio of novel and proprietary oral drug delivery technologies as well as a late-stage pipeline of innovative extended release ("XR") products for attention deficit hyperactivity disorder ("ADHD"), announced today the completion of the acquisition of all of the commercialization and profit rights to its hydrocodone polistirex and chlorpheniramine polistirex extended release suspension product from its collaboration partners Chiesi USA, Inc., and Coating Place, Inc.

The antitussive/antihistamine combination product is a generic equivalent of the product currently sold under the Tussionex® brand name. The product is indicated for the relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children six years of age and older. According to Symphony Health Solutions, a third-party provider of prescription data, there were approximately 2.5 million total prescriptions of Tussionex® and related generic products in 2013.

"We are pleased to acquire the full rights to this product, as we believe that there is a significant opportunity to expand our sales

In the News continued on page 36

In the News continued from page 35

given the demand within the market. Antitussives are among the most commonly prescribed medications for the treatment of coughs and colds," said Dr. Vipin K. Garg, president and CEO of Neos. "Establishing a commercial presence is a natural progression for Neos as its late-stage ADHD pipeline moves forward in the approval process," he added.

"This transaction is in alignment with our strategy to focus our growth of the company in the hospital and related specialty markets," said Ken McBean, president of Chiesi USA. "We are pleased that Neos, our manufacturing partner for the product, will now have the opportunity to also market this product."

"We are committed to continuing our relationship with Neos as its exclusive supplier of the drug resin complexes used in the suspension," added Tim Breunig, CEO of Coating Place, Inc.

Rexahn Receives a Notice of Allowance from the U.S. Patent and Trademark Office for a Novel Targeted Cancer Drug Delivery Platform

Business Wire: September 3, 2014 – ROCKVILLE, MD, U.S.A. – Rexahn Pharmaceuticals, Inc. (NYSE MKT: RNN), a clinical stage biopharmaceutical company developing best-in-class therapeutics for the treatment of cancer, today announced it has received a notice of allowance from the U.S. Patent and Trademark Office for a new delivery technology titled "Polymeric Systems for the Delivery of Anticancer Drugs." The patent covers CPMA, a new polymer drug delivery platform technology developed by Rexahn.

"We are pleased to further expand our platform of proprietary drug delivery technologies in preclinical development. CPMA complements our nano-polymer-drug delivery platform, nano-polymer-drug conjugate system (NPDCS), which has already shown promising results in preclinical studies," stated Rexahn's CEO, Peter D. Suzdak, Ph.D. "Our drug delivery platforms address a well-recognized need in cancer treatment for drugs that selectively target and kill cancer cells, while leaving healthy cells unharmed. Although numerous widely used FDA-approved anticancer drugs offer benefits to patients, in most cases, the efficacy of these drugs can be significantly improved, and their toxic side-effects minimized, if they can be combined with a targeted drug delivery technology to bring the drug directly into cancer cells."

The CPMA technology platform allows for multiple anticancer compounds to be covalently bound to the proprietary polymer backbone and be coupled to a signaling moiety. The signaling moiety directs the bound drug to the cancer cell, thereby bypassing healthy cells leading to enhanced efficacy with the potential for reduced side effects. Once inside the cancer cell the CPMA complex is metabolized, yielding the free anticancer compound. Because of its diverse chemical properties, CPMA is highly water soluble, which allows water-insoluble anticancer compounds to be bioavailable through a more effective delivery.

CPMA is a polymer-based drug delivery platform for the targeted delivery of anticancer compounds directly to cancer cells. The highly versatile chemical properties of CPMA allow it to be covalently linked to a diverse range of anticancer compounds together with a signaling moiety directing it to cancer cells and bypassing healthy tissues. Once inside a cancer cell, covalent linker is metabolized, yielding the free anticancer compound. CPMA has the flexibility to covalently bind multiple anticancer compounds into a signal formulation. Because it is highly water soluble, CPMA also enables compounds that are water insoluble to be more effectively delivered and bioavailable.

NPDCS is a nano-polymer targeted anticancer drug delivery platform. Rexahn's first clinical candidate for NPDCS is RX-21101, which combines its nano-drug delivery system with docetaxel, a widely used FDA-approved chemotherapeutic agent. RX-21101 may bolster efficacy while lowering toxicity of docetaxel and other FDA-approved drugs through specific tumor targeting and improved deliver to the tumor site. Potential indications include breast, ovarian, prostate, and lung cancers.

Rexahn Pharmaceuticals is a clinical stage biopharmaceutical company dedicated to developing best-in-class therapeutics for the treatment of cancer. Rexahn currently has three clinical stage oncology candidates, Archexin®, RX-3117, and Supinoxin™ (RX-5902), and a robust pipeline of preclinical compounds to treat multiple types of cancer. Rexahn has also developed proprietary drug discovery platform technologies in the areas of nano-polymer-drug conjugate systems (NPDCS), CPMA, 3D-GOLD, and TIMES. For more information, please visit www.rexahn.com. ■

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Calendar of Events

2015

4th Drug Formulation & Bioavailability
January 26–28
Boston, MA, U.S.A.
http://exlevents.com/4th-drug-formulation-bioavailability/

CRS Germany Local Chapter Meeting
Sponsored by CRS
February 12–13
Muttenz, Switzerland
www.controlledreleasesociety.de

Society for Biomaterials
April 15–18
Charlotte, NC, U.S.A.
http://2015.biomaterials.org

2015 CC-CRS/CSPS Joint Conference
Sponsored by CRS
May 26–29
Toronto, Canada
http://cc-crs.com/CRS

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

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

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