

### What's Inside

42nd CRS Annual Meeting & Exposition: Ways to Connect

Large-Scale Production of Cosmetic Hesperidin Nanocrystals

Folate-Decorated Nanoparticles Show Prolonged Antiangiogenic Activity in Retinal Pigment Epithelium Cells

Interview with Richard Guy

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Patent Watch



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### Table of Contents

From the Editor
From the President
Interview Unraveling the Legacy of Richard Guy, Professor of Pharmaceutical Science from the University of Bath
2015 CRS Annual Meeting
<b>Scientifically Speaking</b> Large-Scale Production of Cosmetic Hesperidin Nanocrystals by smartCrystal® Technology
Folate-Decorated Nanoparticles Exhibit Size-Dependent Internalization and Prolonged Antiangiogenic Activity in Retinal Pigment Epithelium Cells
<b>Preclinical Sciences &amp; Animal Health</b> Review of the Joint CRS-AAPS Workshop in Animal Health Drug R&D: Formulation, Delivery and Development to Market (San Diego, November 1–2, 2014)
<b>Volunteer Spotlight</b> Making a Commitment to Volunteering: Ian Tucker
Chapter News CRS University of Missouri–Kansas City Student Chapter
What's on Board? CRS Election Results
Greetings from Around the Globe
Patent Watch
In the News
Calendar of Events Cover 4

### Advertisers' Index

Formulation, Processing, and Testing of Functionally Coated	
Multiparticulates Workshop	23
Drug Delivery and Translational Research	Cover 3

### From the Editor

#### Editors

Charles Frey Steven Giannos Arlene McDowell Bozena Michniak-Kohn Yvonne Perrie Rod Walker

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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### Dear Reader,

It has been a busy few months for CRS. We have had our elections (see inside for results) and have been finalising the preparations for our annual meeting. We have also been celebrating the global reach of CRS—have a look at our editors' pictures on page 22, and share your photos on Twitter using #CRSglobal. Looking forward to our annual meeting and completely without bias, I must say that it is going to be a fantastic conference—great science in one of the best cities in the world (OK, I may be a tad biased regarding the location). When people think of Scotland, often they think of mountains, whisky, Irn Bru, bagpipes, men in skirts (wearing no underwear, naturally), and deep-fried food. Indeed this is all true but, like everywhere, there is more to Edinburgh than first meets the eye, so hopefully you will enjoy the city and it will foster new research collaborations and ideas. However, to truly embrace the heritage, perhaps consider the following phrases for the questions/discussions during the science sessions to liven things up.

#### Phrase Translation Gie it laldy Give it your all Keep calm Keep the heid Haud yer wheesht Please be quiet Please turn off your mobile phones Switch yer phone aff Gonnae no' dae that Please don't do that Ye mak a better door than a windae Can you move over please, I cannot see the presentation Good question, I don't know Ah dinnae ken Yer aff yer heid You're crazy, your results don't prove that Yer at it Your talking nonsense Awa an bile yer heid Don't make such silly suggestions to me Yer a numpty You're an idiot No ah umnae No, I am not Yer an awfy blether Could you finish your presentation please now, your time is up. Yer a chancer You're pushing your luck Sen fur the polis Call the police A cannie wee scientist That person is a smart scientist That wiz a belter That was a great presentation Galas talk Great talk Pure dead brilliant results Really good results Ya dancer Hooray That session was very busy That session was hoachin

I look forward to hearing the discussions at the meeting. And remember, don't ask a Scotsman what is worn under his kilt, as the politest response you will probably get is "nothing is worn: it's all in perfect working order."

Cheerio the noo, Yvonne ■



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

### **Strategic Planning**

As I near the end of my time as CRS President, I am enjoying this final sprint to our annual meeting in Edinburgh. Like I imagine for the previous 35 presidents, I have primarily had an enjoyable and productive time. As with all of life's moments, the primary positives have been the people. The Board, committees, chapters, our incredible team at headquarters, and members—all of these have been what has created the memories this past year for me.

In mid-April we held a meeting of the executive board in Nottingham. We selected Nottingham for this meeting to dovetail with the annual chapter meeting of the United Kingdom-Ireland Local Chapter (UKICRS). The UKICRS meeting was spectacular thanks to the efforts of organizers Maria Marlow and Laura Mason and to the strong chapter headed by Gavin Andrews. For the Board to immerse ourselves in the local meeting was the ideal way to prepare for the next two days of strategic planning.

Our society is strong, but we have challenges. A review and renewal of our strategic plan is the correct course for us to advance as vibrantly as possible beyond 2015. Here is a link to our current strategic plan: www.controlledreleasesociety.org/ about/leadership/Pages/StrategicPlan.aspx

At our meeting we committed to several items:

- We will update our strategic plan in the second half of 2015. As appropriate, this is a living document and needs to evolve to continue to serve our dynamic membership.
- We will remain focused on our signature annual meeting. We have made a number of changes that will be apparent in Edinburgh and are enthused about the renewed meeting. Still, we think there is room for more improvement, primarily in terms of education and more industry involvement.
- We are fortunate to have many engaged volunteer members. We will continue to recruit new leaders to key roles, particularly committee heads. We will work more closely between the Board and key committees to make sure that all are engaged and on task. We will consider a new committee organization.
- We will begin a focus in advance of each annual meeting with the local community. This will include our members but, for example, we will also reach out to local leaders in Seattle over the next few months in advance of our 2016 meeting.
- We will continue to capitalize and expand our ventures in publishing such as *Drug Delivery and Translational Research* and our book series.
- With the incredible content we have as the leading voice for delivery science and technology via our journals, books,

newsletter, and annual meeting, we will look to find ways to expand the link between content and engaged members.

• We will look to expand sales and marketing to ensure that more people know about CRS.

# Please read the current strategic plan, and let the Board know your thoughts and how you want to help!

As you know from the earlier announcement, we have elected a new Board and Board of Scientific Advisors (BSA). My congratulations to all nominees, and to the winners, for the Board: Ruth Schmid as President-Elect, Christine Allen as Treasurer-Elect, Ben Boyd as Secretary, and Justin Hanes and Nicole Papen-Botterhuis as Directors-at-Large. We are also welcoming new BSA members Daniel Bar-Shalom, Craig Bunt, Peter Cheifetz, Michael Doschak, Hideyoshi Harashima, Arlene McDowell, and Arto Urtti. I am also pleased to announce that we will induct five new members of the College of Fellows in Edinburgh: Hamid Ghandehari, Edith Mathiowitz, Samir Mitragotri, Yvonne Perrie, and Thomas Rades.

As you know from previous communications, we are planning a tremendous meeting in Edinburgh. I want to again emphasize a few. Imagine a lunch with luminaries from the history of our field, Nicholas Peppas and Vince Lee (only about 10 tickets remain!) on Tuesday of the annual meeting. Imagine a reception in a UNESCO World Heritage site with the tastes and sounds of Scotland. Imagine almost twice the number of posters as last year in Chicago (937 versus 495—the highest ever!). And imagine a dynamic meeting with sessions set up to create a dialog between academic and industry members. Better yet, don't imagine it, just plan to be in Edinburgh on July 26–29!

My day job is with a 74-year-old organization, Southern Research. I have two buildings on my campus named for Charles Kettering, who was a benefactor of our organization. As I have started to educate myself into the history, I found what an incredible research leader Kettering was, with a career primarily at General Motors. He is immortalized in a number of named entities, most notably Memorial Sloan Kettering Cancer Center. We published a memorial to him when he passed away in 1958, and as I read it I was touched by a quote of his:

"Research is a high-tech work that scares a lot of people. It needn't. It is rather simple. Essentially, research is nothing but a state of mind—a friendly, welcoming attitude toward change."

So join me as we look toward change—whether a renewed strategic plan or a reinvigorated annual meeting. I look forward to that change with you, in the friendly, welcoming way that is CRS. ■

# Unraveling the Legacy of Richard Guy, Professor of Pharmaceutical Science from the University of Bath

Vishwas Rai<sup>1</sup> and Bozena B. Michniak-Kohn<sup>2</sup>



Dr. Richard Guy is a professor of pharmaceutical science at the University of Bath, United Kingdom. With over 20 years of experience in academia and industry, and having published over 350 peer-reviewed articles, 70 book chapters, coauthored or coedited several scientific books, and coinvented multiple patents, he has made his mark in the field of pharmaceutical sciences.

Richard Guy.

He received an M.A. in chemistry from Oxford University (1977) and his Ph.D. in pharmaceutical chemistry from the University of London (1980). He has held academic posts at the University of California, San Francisco (UCSF, 1980–1996) and the University of Geneva (1996–2004). In 2004, he joined the University of Bath as a professor of pharmaceutical sciences.

Dr. Guy's research focuses on skin barrier function and characterization, transdermal drug delivery, enhancement of percutaneous absorption, iontophoresis, noninvasive biosensing, and the prediction and assessment of skin penetration and topical bioavailability. He maintains an active research laboratory at the University of Bath. His current research projects include measurement of the skin's biomechanical properties at the nanoscale using atomic force microscopy; exploring in vitro-in vivo correlations to facilitate the determination of topical drug product bioavailability and bioequivalence; the potential of polymeric film-forming systems as sustained release platforms for topical drugs; determination of the disposition of drug and formulation excipients (including nanoparticles) post application to the skin using coherent Raman scattering and confocal microscopy; development of an integrated iontophoretic delivery system for buprenorphine and naltrexone to treat polydrug abuse; examination of a graphene-based biosensor for noninvasive, transdermal glucose monitoring; quantification of dermal absorption from pesticide residues from treated plant surfaces; and derivation and evaluation of predictive models of percutaneous penetration for pharmaceutical and cosmetic "actives," and for potentially toxic chemicals, that come into contact with skin.

Dr. Guy is an elected fellow of the Royal Society of Chemistry, American Association of Pharmaceutical Scientists, American Association for the Advancement of Science, Academy of Pharmaceutical Sciences, and the CRS College of Fellows. He has received numerous awards including the APV (International Association for Pharmaceutical Technology) Award for Outstanding Achievements in the Pharmaceutical Sciences (2000). He was the first recipient of the CRS Young Investigator Award (1988) and later served as president (2000– 2001); recently, he received the CRS Founders Award (2013).

Prof. Guy is a member of the editorial advisory boards of several journals including the *Journal of Pharmaceutical Sciences* and the *European Journal of Pharmaceutics and Biopharmaceutics*. He also serves as a consultant and scientific advisor to a number of pharmaceutical, cosmetic, and biotechnology companies in Europe and the United States.

### Q How and when did your research navigate toward the dermaceutical (skin) area?

A At Oxford, my final-year research project involved the measurement and mathematical modelling of radial drug diffusion in the dermis. I undertook *in vivo* experiments on myself and followed the lateral transport of a compound that elicited vasodilation of the cutaneous microcirculation. It was pure luck that I worked on this particular project—a labmate had been assigned this research, but he turned out to be much less sensitive than me to the vasodilatory effect of the compound, and so we swapped projects! The rest, as they say, is history.

#### Q Can you tell us what research you conducted for your doctoral thesis?

A My Ph.D. research was strongly physical chemical, with a focus on relatively precise determinations of interfacial transport phenomena and the diffusivity of "interesting" molecules of biological and pharmaceutical relevance. In parallel, I began what became a longstanding collaboration and friendship with Jonathan Hadgraft, and we published a series of mathematical modelling papers related to various aspects of percutaneous absorption and drug delivery.

### Q You have been in academia all of your career. Have you ever considered working for the pharmaceutical industry?

A Over the years, I have been approached about the possibility of moving out of academia, but I've never really come close to making the jump, so to speak. That is not to say that I haven't enjoyed excellent relationships with the pharma, cosmetic, and personal care industries, both in terms of generously funding research in my laboratory as well as frequently acting as a consultant and scientific advisor (an activity that is enjoyable, challenging, and ongoing).

<sup>&</sup>lt;sup>1</sup> Chrono Therapeutics Inc., Hayward, CA, U.S.A.

<sup>&</sup>lt;sup>2</sup> Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, U.S.A.

- Q What recommendations would you have with all your current experience for young scientists starting their careers in academia?
- A First of all, be well prepared, by which I mean think strategically about where to undertake your Ph.D. research and where to find a productive and educational postdoctoral experience. I am of such an old vintage that a postdoc was not de rigueur when I finished my Ph.D., and I went straight from my oral examination directly to a post as an assistant professor in the United States with a two-week holiday in between! That's not likely to happen today, and a postdoc is an essential criterion to get one's foot on the academic ladder. Second, steel yourself for disappointment and a long lag time before things start to take off. I'll always be immeasurably grateful to my senior colleagues at UCSF for their patience and for allowing me the time necessary to establish myself as a truly independent investigator. This was really important because those letters informing you that your grant application was not successful will be a strong test of your resilience and will to succeed. Third, the "good old days" of academics operating on a diet of three-year one-man-and-his-postdoc research grants are pretty much over (rightly so, I believe), and larger, collaborative projects are becoming the norm. Involvement in such multidisciplinary research programs is a good thing and is nowadays the most likely path to the forefront of one's chosen area of specialism.
- Q How many of your past doctoral and postdoctoral students have gone to academia and how many have gone to industry (approximately)?
- A Of my doctoral students, the distribution is 23 industry, 6 academic, and 7 elsewhere (e.g., regulatory). For the postdocs, 22 are in industry, 22 in academia, and 7 elsewhere.
- Q You moved your research group several times. Can you comment on the motivations for your moves (United States, Geneva, and Bath)?



In academic regalia, congratulating graduates.

A Well, after finishing my Ph.D., I've held academic posts in three places, which means only three moves! Going to the United States was a big step to take back in 1980. My Ph.D. advisor, who had seen how the system worked over there while on sabbatical, was not a fan of the tenure-track system and the competitive business of acquiring grant support, and he counselled me to think hard about leaving the United Kingdom. However, after a gruelling interview process at what has been the top school of pharmacy in the United States forever, and having been seduced by San Francisco, I knew that I was going to give it a shot. I was 25 when I was appointed, and I've never regretted the decision to go-as things turned out, I don't think that I could've made a better choice. That having been said, leaving UCSF 16 years later was not easy. However, many things had changed in that time, and the people in Geneva put together an exciting offer that promised much potential. By then, my research was pretty well established, and the opportunity to direct the science in a new research centre, backed by what was then a very strong team of pharmaceutical science academics in Switzerland, was extremely attractive. The eight years I spent there were tremendous fun (especially for the students who found my lectures in French to be particularly amusing) and remarkably productive. What then led to my final move to Bath after half a lifetime working away from England? Again, a new opportunity (in another beautiful city) in one of the best departments of pharmacy in the United Kingdom. On this occasion, the attraction was a dynamic environment with colleagues across the Faculty of Science eager to collaborate on a range of interdisciplinary research projects and a willingness, in particular, to encourage and develop new, young faculty.

# Q Any recommendations for faculty thinking of making transatlantic moves? How difficult was it, and any tips from your experiences?

A Any move demands careful reflection, and a decision to go must be made with an absolute commitment to succeed and without looking back. One must also have a realistic understanding that there will be a period of diminished productivity and moments of frustration (especially with university, city, and national bureaucracies!) that will try the patience of a saint. Of course, I moved to the United States a long time ago, and life is quite different now than it was in the early 1980s (before biotech, HIV, email, and so on!). Nonetheless, some aspects will not have changed. First, Americans are definitely different from (for example) the British, and the United States is not the same as Europe. Expecting otherwise, and bemoaning the fact that "that's not how we do it," is definitely unproductive and will not endear one to the locals, so to speak. The contrasts, and the obvious fact that there are often multiple ways of achieving the same objective, have been (at least, for me) among the most interesting facets of living abroad. Intriguingly, on the other hand, the tension between university academics and administrators is a global phenomenon, and I've yet to find an institution where either set of individuals is entirely happy with the other!

Interview with Richard Guy continued from page 5

Q What changes in pharmaceutical research trends have you observed in the last decade? How do you see the field progressing in the near and distant future?

A Many areas come immediately to mind, but I'll just pick three. First, and very broadly speaking, is the evolution of nanoscience. Impact on the pharmaceutical sciences (and the pages of publications such as the Journal of Controlled Release) is self-evident, and most of us in the drug delivery business have written papers and grant proposals where the prefix "nano" has been liberally used. While this is certainly a popular domain for academic research, its translation to practicality is less certain (and, it must be said, at least some of the challenges faced may be anticipated by liposomal history, so to speak). Second, tissue engineering has moved from science fiction into the real world, with a trajectory that seems to be steeper every year. This coming together of biology and engineering seems to me to be one to watch closely in the future. Third, the growing number of macromolecular drugs that are reaching the market and proving to be both clinically and commercially successful is a development that seems likely to throw attention back onto the drug delivery community once again. In the skin area, of course, we have already seen the advent of various "poration" technologies to circumvent the barrier-the question now is whether any approach can be competitive, therapeutically and economically, with a needle and syringe!

Q Please share several of the most influential research publications coming out of your research lab. What was the impact of these research articles in the field?

A I'd have to start with my most-cited article, coauthored with Russ Potts, describing the derivation of our algorithm (rather embarrassingly known these days as the "Potts & Guy" equation) to predict the skin permeability of chemicals. This approach is used rather widely these days to calculate  $k_p$  values and to estimate chemical flux rates across the skin.



Playing cricket.

Potts, RO, Guy, RH. Predicting skin permeability, Pharm. Res. 9: 663-669 (1992).

Next would be a paper to represent a body of work related to the use of iontophoresis to extract information noninvasively across the skin for the purposes of monitoring and diagnosis. Our fundamental work on electro-osmosis in this regard (e.g., Delgado-Charro and Guy 1994) was behind the principle of the GlucoWatch<sup>®</sup> Biographer, which remains, even today, the only noninvasive glucose monitor to have been approved by the U.S. FDA.

Delgado-Charro, MB, Guy, RH. Characterization of convective solvent flow during iontophoresis, Pharm. Res. 11: 929-935 (1994).

Rao, G, Guy, RH, Glikfeld, P, LaCourse, WR, Leung, L, Tamada, J, Potts, RO, Azimi, N. Reverse iontophoresis: Noninvasive glucose monitoring *in vivo* in humans, Pharm. Res. 12: 1869-1873 (1995).

Much of the research from my group has been underpinned by physicochemical principles and mathematical modelling. In so doing, we have been able to provide insight into skin barrier function that has complemented nicely the work of my more biologically oriented colleagues! Here are two favourite publications.

Kalia, YN, Pirot, F, Guy, RH. Homogeneous transport in a heterogeneous membrane: Water diffusion across human stratum corneum *in vivo*, Biophys. J. 71: 2692-2700 (1996).

Pirot, F, Kalia, YN, Stinchcomb, AL, Keating, G, Bunge, AL, and Guy, RH. Characterization of the permeability barrier of human skin *in vivo*, Proc. Natl. Acad. Sci. U.S.A. 94: 1562-1567 (1997).

At the same time, we have made good use of spectroscopic techniques and imaging tools to unravel mechanistic information about chemical transport mechanisms across the skin and nail barriers at the molecular level. Significant contributions have applied infrared spectroscopy and confocal microscopy, and more recent work has taken advantage of progress in atomic force microscopy and coherent Raman scattering. Here are two examples (one older and two newer).

Naik, A, Pechtold, LARM, Potts, RO, Guy, RH. Mechanism of oleic acid-induced skin penetration enhancement *in vivo* in humans, J. Controlled Release 37: 299-306 (1995).

Saar, BG, Contreras-Rojas, LR, Xie, XS, Guy, RH. Imaging drug delivery to skin with stimulated Raman scattering microscopy, Mol. Pharm. 8: 969-975 (2011).

Chiu, WS, Belsey, NA, Garrett, NL, Moger, J, Delgado-Charro, MB, Guy, RH. Molecular diffusion in the human nail measured by stimulated Raman scattering microscopy, Proc. Nat. Acad. Sci. U.S.A., www.pnas.org/cgi/doi/10.1073/ pnas.1503791112 (2015). Finally, a research focus for many years has been the assessment and optimization of topical drug bioavailability. Here we have applied many of the tools mentioned above to explain why drug delivery into the skin is so inefficient and what might be done to improve the situation. In this regard, our work has attracted significant attention from both industry and the regulatory agencies, especially the U.S. FDA. I'm particularly proud of our efforts in this area, exemplified by the following two publications.

Herkenne, C, Naik, A, Kalia, YN, Hadgraft, J, Guy, RH. Dermatopharmacokinetic prediction of topical drug bioavailability *in vivo*, J. Invest. Dermatol. 127: 887-894 (2007).

N'Dri-Stempfer, B, Navidi, WC, Guy, RH, Bunge, AL. Improved bioequivalence assessment of topical dermatological drug products using dermatopharmacokinetics, Pharm. Res. 26: 316-328 (2009).

Q Please share several research publications (outside of your research) that have had the most influence in shaping the related pharmaceutical field.

A In 2013, I wrote an article in a special issue of the journal *Skin Pharmacology & Physiology* (26: 181-189) that was dedicated to a pioneer in the field, Robert Scheuplein. The paper recounts my "take" on what I believe was a golden era of skin barrier research and cites most of the articles that made a profound impact on the way I have thought about my research. Here are five stand-out publications from my list of references.

Scheuplein, RJ. Mechanism of percutaneous adsorption. I. Routes of penetration and the influence of solubility, J. Invest. Dermatol. 45: 334-346 (1965).

Michaels, AS, Chandrasekaran, SK, Shaw, JE. Drug permeation through human skin: Theory and *in vitro* experimental measurement, AIChE J. 21: 985-996 (1975).

Potts, RO, Francoeur, ML. Lipid biophysics of water loss through the skin, Proc. Natl. Acad. Sci. U.S.A. 87: 3871-3873 (1990).

Flynn, GL, Dürrheim, H, Higuchi, WI. Permeation of hairless mouse skin II: Membrane sectioning techniques and influence on alkanol permeabilities, J. Pharm. Sci. 70: 52-56 (1981).

Kasting, GB, Smith, RL, Cooper, ER. Effect of lipid solubility and molecular size on percutaneous absorption.

Pages 138-153 in: Skin Pharmacokinetics (Pharmacology and the Skin, vol. 1). Shroot, B, Schaefer, H, eds. Karger: Basel, Switzerland (1987).

Younger scientists take note: the most recent paper in my list is 1990! There is good stuff to be found in the literature, even work that was performed before you existed. Recognising this fact will prevent episodes of "wheel re-invention."

Q Multiple projects from your laboratory (including examination of a graphene-based biosensor for noninvasive, transdermal glucose monitoring and integrated iontophoretic delivery system for buprenorphine and naltrexone to treat polydrug abuse) have direct implications in the field of medical devices. Please explain the possibilities from your perspective.

A Iontophoresis is a mature technology, the science behind which is well understood. The method has led to the development and regulatory approval of a number of products, but none have yet proved to be commercially viable. I remain optimistic, however, that this situation can be turned around; for example, the anticipated relaunch of the fentanyl iontophoretic system is eagerly awaited. We continue to explore the potential of iontophoresis for both drug delivery and noninvasive monitoring. The buprenorphine-naltrexone project involves an attempt to codeliver, via a single route of administration, two drugs that are presently given sublingually and orally in separate doses. We believe that the principle is valid: funding further in vivo work and subsequent development is more challenging. The graphene-based biosensor for transdermal glucose monitoring is a new attempt to attack a favourite problem of my group, and draws on mechanistic information about the existence of low-resistance pathways across the skin. I think the idea is sound-whether the objective can be realised practically is a work-in-progress (and a lot of fun). It's worth pointing out that, while my lab brings know-how in iontophoresis to these projects, neither would have got off the ground without the collaborations we have in place with colleagues in chemistry, pharmacology, and physics.

#### Q What are your current career aspirations?

A Simply put, to do good science with capable colleagues and to train individuals who will make more important research contributions than I have done. I won't be changing fields, but I'm always on the lookout for new applications of our skill set and incorporating new techniques to address questions that have heretofore proved unanswerable. Because of the nature of the pharmaceutical sciences, our research has always been of an applied nature, and this is unlikely to change, especially as "impact" is a word now stamped on every academic's forehead!

# **2015 CRS ANNUAL MEETING**

# Muly 26-29 Edinburgh, Scotland DE BORE

The 42nd CRS Annual Meeting & Exposition is the **must-attend event** in delivery science and technology. This year's program has been reshaped with a greater focus on member interests, increased industry participation, and more time for active discussion.

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# Large-Scale Production of Cosmetic Hesperidin Nanocrystals by smartCrystal® Technology

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### Introduction

The potent antioxidative effect of flavonoids can be used in cosmetic products to prevent skin from aging and wrinkles, provided a sufficiently high skin penetration can be obtained by the dermal formulation. Cosmetic products can be gel, cream, or lotion. However, the poor water solubility of this kind of active will limit the application because of the consequently low skin penetration and absorption. Nanocrystals for increasing the oral bioavailability are meanwhile also dermally applied to improve the penetration into the skin. Cosmetic products have been on the market since 2007 (for example, Juvena in the Juvedical line since 2007 and Platinum Rare cream by La Prairie since 2009).

The improvement of the skin penetration of poorly soluble actives by nanocrystals is caused by three effects:

- 1. The increased saturation solubility of the active (in terms of the Kelvin equation) generates a higher concentration of the active in the formulation on the skin and, subsequently, a higher concentration gradient between the formulation and skin.<sup>1</sup>
- 2. The nanosized particles have a high contact area to the skin, are adhesive, and have a long residence time.<sup>2</sup>
- 3. The small size leads to follicular accumulation of the nanocrystals, promoting absorption and forming a depot.<sup>2</sup>

Two main methods, bead milling and high-pressure homogenization, can be used in production of nanocrystals on a large industrial scale. Bead milling has been widely applied in the pharmaceutical industry (e.g., Nanosystems/Élan, now part of

Table 1. Compositions of Nanocrystal Concentrate and MarketedDilution of the Nanosuspension (18 kg Batches)

Component	Proportion	
Concentrate (w/w)		
Active	18%	
Surfactant	1% Poloxamer 188	
Preservative	1% Euxyl PE9010	
Water for injection	80%	
Dilution (w/w)		
Active	5%	
Surfactant	1% Poloxamer 188	
Preservative	1% Euxyl PE9010	
Glycerol 87%	5%	
Water for injection	88%	

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Alkermes, U.S.A.), being a low-energy process. High-pressure homogenization was developed as an alternative process in the 1990s to produce nanocrystals with high energy input, allowing also aseptic production (SkyePharma, U.K.; Baxter, U.S.A.).

The newly developed smartCrystal<sup>®</sup> technology combines bead milling with high-pressure homogenization (PharmaSol, Germany).<sup>3,4</sup> In this study hesperidin nanocrystals were produced on a large scale as commercial nanocrystal concentrate for incorporation into cosmetic products. Highly concentrated nanosuspension was produced by bead milling first. This intermediate product was then diluted to the final market product concentration (5%) and processed by high-pressure homogenization.

#### **Experimental Methods**

Coarse suspension (batch size 18 kg) of hesperidin (Table 1) as the intermediate concentrate was passed five times through a Bühler PML-2 bead mill (Bühler, Switzerland) with a 1,050 mL milling chamber. Yttrium oxide stabilized zircon oxide beads of 0.4–0.6 mm diameter (Hosokawa Alpine, Germany) were used as the milling medium. Milling rotator speed was 2,000 rpm, and pump capacity was 10%. During the production, the milling chamber was cooled at 5°C. The size of nanocrystals was monitored during the milling after each passage. The milled product obtained after five passages was diluted (Table 1) and homogenized with an Avestin C50 homogenizer (Avestin, Canada), applying one cycle at 500 bar to obtain the final market product (Figure 1).

Contents of active and preservative in the final product were measured by HPLC. Size analysis was carried out by photon



**Figure 1.** Schematic diagram of the production process of smartCrystal<sup>®</sup> technology producing hesperidin nanosuspension.<sup>5</sup>

correlation spectroscopy (PCS) (Zetasizer Nano ZS, Malvern Instruments, U.K.), laser diffractometry (LD) (Mastersizer 2000, Malvern Instruments), and light microscopy (Ortoplan, Germany).

### **Results and Discussion**

Bead milling led to a steady decrease of the size after each passage (from 1 to 5, Figure 2). After only one passage, the PCS diameter was decreased to 539 nm. However, the existence of large particles was detected by LD, as the diameter d(v)50% was still 1.748 µm. After the fifth passage, the PCS diameter decreased to around 290 nm with a polydispersity index (PdI) of 0.237. The decrease of median LD diameter d(v)50% from passage 2 to passage 5 was minor, but the d(v)90% became lower than 1.5 µm (Figure 2). This result indicates a very small remaining fraction of larger particles in the intermediate product, which would be unproblematic for a dermal product.



**Figure 2.** Photon correlation spectroscopy (PCS) diameter and polydispersity index (PdI) (upper), and laser diffractometry (LD) diameters 50, 90, and 99% (lower) obtained from the bead mill as function of passages 1–5.

The intermediate product was diluted to 5% hesperidin and processed by high-pressure homogenization. PCS size of the final market product was 265 nm with an LD diameter d(v)99% less than 4  $\mu$ m (before this step, 290 nm and 4.205  $\mu$ m). This decrease in size proved that the subsequent high-pressure homogenization could generate further size reduction. In addition, the size distribution was more homogenous owing to the removal of larger particles and aggregates.

The chemical contents of hesperidin and Euxyl PE 9010 were 4.9 and 1.0%, respectively, which was nearly identical to the theoretical content and was highly acceptable considering typical variations in large-scale production.

#### Conclusions

Processing parameters for a large-scale production process for hesperidin nanocrystals were established based on the smartCrystal<sup>®</sup> technology. The batch size of 18 kg of intermediate concentrate (which corresponds to 65 kg of marketed product) can be increased by simply multiplying the volume of suspension passing the bead mill during each passage. The process with the Bühler PML-2 bead mill can be run cost-effectively and can be fully automated 24 h a day. By combining bead milling and highpressure homogenization, a product with increased physical stability is obtained compared with using only one of the milling processes.<sup>3</sup> This observation is of interest for dermal products, which often contain electrolyte-type ingredients, impairing the physical stability by zeta potential reduction.

#### Acknowledgements

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# Folate-Decorated Nanoparticles Exhibit Size-Dependent Internalization and Prolonged Antiangiogenic Activity in Retinal Pigment Epithelium Cells

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### Background

Retinal pigment epithelium (RPE) is a target site for drug delivery to the posterior segment of the eye. The dysfunction of RPE plays an important role in the pathological development of ocular diseases, such as age-related macular degeneration (AMD). In AMD, abnormal RPE cells trigger choroidal neovascularization by the secretion of vascular endothelial growth factor (VEGF). On the other hand, folic acid (FA) is actively transported by RPE cells via folate receptors, which are only present in this cell layer in the retina.

Based on this knowledge, we formulated folate-decorated nanoparticles (NPs) (Figure 1) using folate receptors as specific portals to deliver therapeutics to RPE cells. Triamcinolone acetonide (TA) was chosen as the model drug in our study because of its well-known ability to inhibit blood vessel growth by suppressing VEGF and promoting pigment epithelium derived factor (PEDF). Folate-modified polyethylene glycol-bpolycaprolactone (folate-PEG-b-PCL) was used as the building block of NPs. Driven by hydrophobic interaction, TA molecules are sequestered in the PCL-rich core. Because PCL undergoes slow degradation by hydrolysis, TA encapsulated was expected to be slowly released into the external medium in its soluble form.

### Method

Synthesis of folate-PEG-b-PCL copolymers was carried out as described previously.<sup>1</sup> Folate-PEG-b-PCL NPs were prepared by nanoprecipitation (Figure 2). To quantify internalized NPs in ARPE-19 cells, Nile red encapsulated folate-decorated NPs were



**Figure 1.** Schematic showing formation of folate-decorated NPs.<sup>2</sup> © John Wiley and Sons; used by permission.

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added to cultured cells for 4 h at 37°C. For inhibition of the cellular pathway, 25  $\mu$ g/mL methyl- $\beta$ -cyclodextran (M $\beta$ CD) (a caveolae inhibitor) or 10  $\mu$ g/mL chlorpromazine (a clathrin inhibitor) was added together with the NPs. After 4 h, cells were washed and then lysed to release the internalized Nile red-loaded NPs for fluorescence detection. Uptake and inhibition kinetics were explored to investigate the selection of endocytic pathway of NPs with different sizes.



Figure 2. A graphical description of the study's methods.

To determine the antiangiogenic effect of TA-loaded folate-PEG-b-PCL NPs, ARPE-19 cells were treated under hypoxia for 24 h to imitate the pathology of ocular angiogenesis. Afterward, fresh medium containing 0.4 mg/mL TA-loaded folate-decorated NPs, TA-loaded non-decorated NPs, or TA was added to cells and incubated under normal oxygen conditions. NP-containing medium was replaced by fresh NP-free medium after incubations with ARPE-19 cells for 2 days. Cell culture medium was replaced every 7 days subsequently. At predetermined time points, cells were harvested and analyzed by real time polymerase chain reaction (RT-PCR). Cells incubated at normal atmospheric oxygen conditions in the same incubator were used as controls.<sup>2</sup>

The uptake kinetics of folate-conjugated NPs in ARPE-19 cells were calculated based on a two-step endocytosis process model. Mathematically, the two-step process can be expressed in the following equation:

### $NP + R \xleftarrow{k_1}{k_2} NP - R \xrightarrow{k_2} NP * + R$

where R represents folate receptors, NP represents folatedecorated polymeric NPs, NP - R represents the receptor-NP complexes on the cell surface, and *NP*\* represents the folate-decorated NPs inside the cells.

After derivations, the following equation was used to estimate the maximum uptake rate and dissociation constant of folatedecorated NPs in ARPE-19 cells under various conditions:

$$\frac{1}{\text{Uptake rate}} = \frac{1}{V_{\text{max}}} + \frac{K_d}{V_{\text{max}}[NP]}$$

#### Results

#### Characterization of Functionalized PEG-b-PCL NPs

Table 1 summarizes the size and zeta potential of the various NPs used in the study.

### Prolonged Release of TA from NPs at Endosomal pH

Release of TA from NPs exhibited a two-phase profile with a faster release rate in an acidic environment (Figure 3).

### Encapsulation of TA in NPs Reduced Cytotoxicity to ARPE-19 Cells

Blank and TA-loaded folate-decorated NPs of all sizes were nontoxic to ARPE-19 cells (Figure 4).

NP	Terminal Functional Group	Mean Size (nm)	Polydispersity (PDI)	Zeta Potential (mV)
NH <sub>2</sub> -PEG-PCL	NH,	53 ± 2.5	0.21	22.8 ± 1.2
2	NH <sub>2</sub>	130 ± 5.5	0.21	$20.4 \pm 2.3$
	NH <sub>2</sub>	232 ± 3.7	0.16	$26.7\pm0.6$
mPEG-PCL	CH <sub>3</sub> O	45 ± 3.5	0.23	$2.8 \pm 1.4$
	CH <sub>3</sub> O	122 ± 2.1	0.19	$2.1 \pm 1.0$
	CH <sub>3</sub> O	$250 \pm 1.1$	0.20	$1.8 \pm 1.6$
COOH-PEG-PCL	COOH	50 ± 2.2	0.18 -	-44.8 ± 3.2
	COOH	121 ± 6.3	0.16 -	$-38.2 \pm 4.4$
	COOH	218 ± 4.4	0.15 -	-46.9 ± 1.4
FA-PEG-PCL	Folic acid	49 ± 4.5	0.20 -	-22.8 ± 2.2
	Folic acid	127 ± 1.7	0.21 -	-21.2 ± 1.7
	Folic acid	244 ± 6.2	0.16 -	-24.6 ± 1.2

#### Table 1. Summary of Size and Zeta Potential of PEG-b-PCL NPs<sup>z</sup>

<sup>z</sup>Table adapted from Suen and Chau (2013).1



Figure 3. Release profile of TA from FA-PEG-PCL NPs (n = 3).

### Folate-Decorated NPs Internalized via Receptor-Mediated Endocytosis

Targeted entry of nanoparticles to RPE cells was achieved by decorating the surface with FA, the preferred ligand of folate receptors. It is known that RPE cells express folate receptors on the cell membrane, and therefore the folate-conjugated NPs can be internalized to RPE cells specifically and efficiently via receptor-mediated endocytosis.

This is supported by the enhanced uptake of nanoparticles with folate modification. The effect was quenched by coincubation with free folate in excess, which competes with folate-decorated NPs for receptor binding (Figure 5).

#### Size-Dependent Internalization of Folate-Decorated NPs

Smaller NPs were internalized via both clathrin-mediated endocytosis (CME) and caveolae-mediated endocytosis (CvME) pathways. Internalization of these smaller particles was a relatively rapid process, showing kinetics reminiscent of receptormediated internalization of ligands. The smallest NPs studied (50 nm) had the fastest internalization rate, and their uptake was dominated by CvME (Figure 6). For 120 nm NPs, the effect



**Figure 4.** Viability of ARPE-19 cells after 1 day and 1 week incubation in medium with TA-loaded PEG-b-PCL NPs and TA suspension (n = 3)(concentration of NPs is 0.4 mg/mL; all groups have the same equivalent concentration of TA at 0.04 mg/mL).<sup>1</sup> © Elsevier; used by permission.



**Figure 5.** Confocal laser scanning microscopy and bright field images of ARPE-19 cells treated with four different NPs after 4 h of incubation at  $37^{\circ}C$  (NP concentration in medium = 0.3 mg/mL).<sup>1</sup> © Elsevier; used by permission.

Scientifically Speaking Suen continued on page 14

#### Scientifically Speaking Suen continued from page 13

of chlorpromazine and M $\beta$ CD on uptake rate was similar. This observation implied that there is no preferred endocytic pathway for 120 nm folate-decorated NPs in RPE cells. When the particle size increased to 250 nm, CvME was primarily responsible for internalization of NPs.

Endocytic pathways of folate-decorated nanoparticles in ARPE-19 cells are dependent on the particle size. Folate-decorated NPs of all sizes tested can be internalized via CvME. This is confirmed by the suppression of maximum uptake rate of nanoparticles by M $\beta$ CD and the low inhibition constant (K<sub>i</sub>) of receptor-NP complexes (Tables 2 and 3).

### Enhanced Antiangiogenic Activities of TA-Loaded Folate-Decorated NPs in ARPE-19 Cells

RT-PCR assay reflected that VEGF was down-regulated (Figure 7) and PEDF up-regulated (Figure 8) following TA treatment. TA-loaded particles not only enhanced the drug effect but extended it for a prolonged period. Furthermore, the comparison between NPs with and without folate modification supported



**Figure 6.** Maximum uptake rate  $(V_{max})$  of 100% folate-decorated nanoparticles of different sizes in ARPE-19 cells at different conditions. Error bars show SD;  $n = 3.2^{\circ}$   $\odot$  John Wiley and Sons; used by permission.

Table 2. Effect of Size of NPs and Presence of Endocytosis Inhibitors on the Dissociation Constant ( $K_d$ ) in ARPE-19 Cells (n = 3)<sup>z</sup>

	Value of K <sub>d</sub> (nM)		
Size of NP	No Inhibitor	Chlorpromazine	ΜβCD
~50 nm	$0.44 \pm 0.31$	$0.91 \pm 0.33$	$1.09 \pm 0.24$
~120 nm	$0.083 \pm 0.030$	$0.059 \pm 0.0.046$	$0.094 \pm 0.014$
~250 nm	$0.0038 \pm 0.0031$	$0.0045 \pm 0.0029$	$0.017 \pm 0.0014$

 $^{\rm z}$  Table adapted from Suen and Chau (2014).²

Table 3. Inhibition Constant (K<sub>i</sub>) of Chlorpromazine and  $M\beta CD$ Against Uptake of Nanoparticles with Varying Size<sup>z</sup>

	Inhibition Constant (nM)		
Size of NP	Chlorpromazine	ΜβCD	
50 nm	$4.96 \times 10^{-2} \pm 0.038a$	$3.46 \times 10^{-3} \pm 1.70 \times 10^{-4}$ ce	
120 nm	$7.24 \times 10^{-2} \pm 0.0060$ b	$1.10 \times 10^{-2} \pm 0.0014$ cd	
250 nm	$3.21 \times 10^{-1} \pm 0.11$ ab	$9.70 \times 10^{-3} \pm 2.50 \times 10^{-4} de$	

<sup>2</sup> Values within the same column followed by different letters are significantly different (P < 0.05) according to *t* test. Table adapted from Suen and Chau (2014).<sup>2</sup>

that the active targeting strategy was effective. By 21 days, TAloaded folate-decorated particles still exhibited a strong antiangiogenic effect. The medium in cell culture was refreshed 2 days after the incubation with drug or drug-loaded NPs. Hence, the prolonged antiangiogenesis activity was owing to drug released from NPs already internalized into the cells. Prolonged release of TA from NPs may be another factor for such a prolonged effect.



**Figure 7.** Effect of hypoxia treatment, TA-loaded NPs, and TA on the VEGF mRNA expression in hypoxia-treated ARPE-19 cells (n = 3). TA-loaded NPs were added to the culture medium of the ARPE-19 cells at a concentration of 0.4 mg/mL. The effective concentration of TA in the TA suspension and TA-loaded NPs was 39 µg/mL. Unpaired t test was performed comparing the TA-loaded FA-PEG-PCL NPs with another TA formulation. \* and \*\* denote P < 0.05 and 0.01, respectively.<sup>1</sup> © Elsevier; used by permission.



**Figure 8.** Effect of hypoxia treatment, TA-loaded NPs, and TA on PEDF mRNA expression in hypoxia-treated ARPE-19 cells (n = 3). TA-loaded NPs were added to the culture medium of the ARPE-19 cells at a concentration of 0.4 mg/mL. The effective concentration of TA in the TA-loaded NPs was 39 µg/mL. Unpaired t test was performed comparing the TA-loaded FA-PEG-PCL NPs with another TA formulation. \* and \*\* denote P < 0.05 and 0.01, respectively.<sup>1</sup> © Elsevier; used by permission.

### Conclusion

Folate-decorated NPs are efficient carriers that utilize both CME and CvME pathways to enter RPE cells upon size variation. Smaller particles of 50 nm are internalized the fastest, with CME as the preferred route. Uptake of 250 nm particles is the slowest and is dominated by CvME. Conjugation of FA enables receptor-mediated endocytosis in RPE cells. The proposed nanocarriers exhibit low cytotoxicity against cultured ARPE-19 cells and have a prolonged release profile of encapsulated hydrophobic drugs, as exemplified by TA. These properties synergistically induced a prolonged antiangiogenesis effect for at least 3 weeks *in vitro*.

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# Review of the Joint CRS-AAPS Workshop in Animal Health Drug R&D: Formulation, Delivery and Development to Market (San Diego, November 1–2, 2014)

David Brayden<sup>1</sup> and Shoban Sabnis<sup>2</sup>

Over 5 years since the last joint workshop on this topic, a total of 48 members of CRS and the American Association of Pharmaceutical Scientists (AAPS) convened in the San Diego Convention Center over two days prior to the main AAPS meeting to discuss a range of topics in animal health pharmaceuticals. The organizers were Shoban Sabnis (Zoetis, U.S.A.), David Brayden (University College Dublin, Ireland), Peter Cheifetz (Merial Limited [A Sanofi Company], U.S.A.), and Michael Rathbone (ULTI Pharmaceuticals, New Zealand). Generous industrial sponsors were Cremer, Scynexis, and Zoetis. The list of speakers and schedule can be located at www.controlledreleasesociety.org/meetings/workshops/Pages/ AnimalHealthWorkshopSchedule.aspx. In the first session David Brayden opened the meeting by reviewing a range of delivery technologies that had crossover value between animal and human health. Several key messages were that innovation in drug delivery is alive and well in animal health, as evidenced by a range of new transdermal sprays for horses that are in trials, novel biocompatible implants, as well as activation inhalers for small animals. On the theme of "One Health," he pointed out opportunities in medical device engineering, also in the study of spontaneous cancers in dogs for developing human and veterinary anticancer agents. While noting the physiological differences between species, there is still informative parallel research in many species examining drug transporters, and these have a role in understanding of pharmacokinetics and in drugdrug interactions. Wendy Collard (Zoetis) reviewed the pharmacology and development of dirlotapide (Slentrol®), a molecule designed to aid reduction in canine obesity. Its mechanism of action was to promote GLP-1 and PPY peptide release from intestinal cells and also to prevent triglyceride-rich chylomicrons formation in enterocytes by potently blocking microsomal triglyceride protein transport (MTP). She went over the development studies in murine models and then in overweight Labradors. The molecule acts locally in the intestine, and its plasma pharmacokinetics predicted gut pharmacokinetics. Ultimately, the oral formulation had issues, which included a large food effect and effects of multiple dosing, leading to variable outcomes in weight loss across breeds. Approved by the FDA in 2007, it is no longer marketed. Izabela Galeska (Merial

Limited) reviewed some of the major long-acting and extended release animal health injectables and discussed the innovation drivers for such products including cost, end-user needs, and socioeconomic factors. She compared the target product profiles for PROHEART-6® microspheres and controlled release steroid implants, as well as *in situ* forming sucrose acetate isobutyrate depots. She then described veterinary case studies of injectable cisplatin beads and depots of recombinant bone morphogenic protein-2. While cost of goods and understanding of the target product profile are essential, she also emphasized the importance of understanding the active pharmaceutical ingredient, allied to novel delivery systems and use of excipients. Raafat Fahmy (FDA) gave a comprehensive analysis of how Quality-by-Design can be used to plan development of modified release oral dosage forms. In his talk, he went over the types of studies and analysis that the FDA will expect to see in animal health submissions.

In the second session, **Steev Sutton** (University of New England) discussed the gastrointestinal (GI) variables in different species including cats, dogs, pigs, rats, and mice.



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).

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<sup>&</sup>lt;sup>2</sup> Zoetis, U.S.A.

These included measures of stomach pH in the fasted and fed state, small intestinal pH, gastric emptying time, GI motility, intestinal permeability, and the role of intestinal transporters. The thesis of the talk was that it is possible to work out if data achieved for an oral controlled release system in one species can be used to predict performance in another. This becomes a highly complex analysis when discussing different canine breeds and oral controlled release dosage forms. In relation to intestinal transporters, Sutton is assembling a biobank to study expression in the GI regions of many species. Marilyn Martinez (FDA) then described a USP initiative to develop methods for solubility testing across species, but especially dogs and cattle. The outputs will include recommendations of methods to determine drug solubility in a target animal species under physiological conditions. She returned to the theme that understanding intestinal physiology between species was the key to calculating the parameters that impact dissolution in vivo. Jane Owens (Elanco) gave an entertaining talk on how the horse can be studied for testing formulations for intraarticular administration of antiarthritic molecules. She went over why the horse is such a useful model for testing formulations that reduce joint inflammation and osteoarthritis; these included low costs compared with several other research species (a surprise to many), high volumes of synovial fluid, MRI imaging, and a panel of established biomarkers of inflammation. One of her conclusions was that equine models would be at the forefront in assessing regenerative therapies and disease-modifying molecules and formulations. The final talk in the session was from Anthony Listro (Foster Delivery Science), who discussed a range of erodible, degradable, and injectable implants in detail. The company is using hot-melt extrusion to provide material for drug-device combinations for human and animal health. He provided data on drug-eluting stents, bioresorbable implants, and drug delivery fibers.

The third session was devoted to the veterinary market, regulatory issues, and innovation. Michael Putnam (Boehringer Ingelheim VetMedica) debated novel production methods. His thesis was based on the increasing needs for animal protein and dairy products and on sales of animal health pharmaceuticals continuing to grow in parallel. With such high volume needs, he discussed how production of such molecules will need to evolve with leaner production and process management. Robert Zolynas, Bayer Healthcare) discussed the challenges of animal health in emerging markets. In an economics-based talk, he discussed the impact of animal welfare and production method changes, demographic shifts in markets, as well as regulatory landscape and market entry strategies. Mai Huynh (FDA) continued the regulatory theme in her talk on injectable controlled release products, which was a counterpoint to the earlier presentation on oral controlled release from Raafat Fahmy; different standards are required for injectables relating to sterility and other criteria, and there are also veterinary productspecific aspects. Brian Carlin (FMC Biopolymers) debated as to why there are so few new excipients emerging. Some of the key points were that there are few incentives for developing pharmaceutical excipients and that there is no "excipient



Panel discussion.

industry" as such, with excipients being solely supplied by chemical subsidiaries of the pharmaceutical industry. He highlighted that lack of innovation in excipient development meant that drug delivery systems were only coming through in an incremental manner rather than with major advances. Still, he noted that there have been some new interesting solubilizing excipients appearing for the first time in products including Captisol®, Solutol® H15, and Soluplus®. He then offered some pointers as to how excipient innovation could be incentivized by reducing the regulatory burden, along with novel pharmacopoeia initiatives and user-supplier initiatives.

The last session focused on research and industrialization challenges. **Dan Peizer** of Catalent gave an informative talk amusingly entitled "New Tricks for Old Dogs" on the Zydis® oral dispersion technology, which is being used in both human and animal health. He described the freeze-dried oral dosage for manufacture, how first iterations can dissolve in three seconds, how other versions are being researched for oromucosal delivery of peptides and proteins, and how taste masking has evolved. Regarding companion animals, Catalent has adapted the technology with flavoring and mucoadhesion capacity, both of which improve compliance from both clients and patients. Praveen Hiremath (Bayer Healthcare) discussed process development, scale-up, and optimization in the veterinary pharmaceutical industry. The take-home message was that skill and attention to detail in this area are just as important as R&D. In the final talk, graduate student Kaushalkumar Dave (South Dakota State University) discussed how to get more young scientists interested in the veterinary pharmaceutical industry, and one of his ideas was for the industry to forge better links with U.S. and international schools of pharmacy by way of sponsoring research symposia and by advocating for increased attention to be given to veterinary pharmaceutical aspects in both school of pharmacy and veterinary school undergraduate curricula. The meeting concluded with a lively roundtable discussion. Feedback for the meeting was very positive, with many responders requesting that the joint CRS-AAPS event should take place on a more regular basis.

# Making a Commitment to Volunteering: Ian Tucker

Society presidents are leaders—respected peers with considerable experience within an organization. Ian Tucker has served as CRS president and this year will complete his term as he steps down from the post of immediate past president. In this Volunteer Spotlight, the Volunteer Recruitment Committee (VRC) wanted to take the opportunity to hear a president's perspective on volunteering with CRS. Arlene McDowell, VRC Immediate Past Chair, interviewed Ian.

### Q How did you get involved in CRS?

- A I attended my first CRS meeting in the 1980s. I didn't know much about the organisation then, but I was told about it by a colleague and mentor from another university who said he had just been to a meeting and it seemed particularly relevant to my research interests.
- Q Please tell us about your current and past volunteering experiences and leadership roles with CRS.
- A Currently I am the immediate past president. In that role, I still have responsibilities to attend all Board meetings (monthly teleconferences and two face-to-face meetings per year); to chair the Nominations Committee, the committee responsible for putting forward to the Board the names of potential candidates for the various roles on the Board (president-elect, secretary, treasurer-elect, and directors-atlarge) and on the Board of Scientific Advisors. I'm also the Board liaison for the CRS Foundation and the College of Fellows Committee. This means I have additional teleconference meetings with those groups, probably four times each per year.

In the past, I was a member of the Board of Scientific Advisors, when it was called the Board of Governors. Then, some years later, I was elected to the Board as a director-atlarge for a three-year term. After a break from the Board, I



Jet boating in New Zealand with Judy Tucker.



Conversations in Chicago during the 2014 CRS Annual Meeting.

was then re-elected as the vice president, a position that no longer exists, and in my year as vice president I was the secretary of CRS. I then progressed to president-elect and finally president in 2013–2014.

### Q What was your most memorable CRS conference and why?

- A It would have to be Chicago 2014, because that was the year I was president and therefore had added responsibilities at the conference. It was held in the vibrant city of Chicago with its fantastic public art works and the enthusiasm of the downtown area, and I did enjoy the "pub quiz" at the banquet. It was fascinating to see all the people who were at the banquet getting excited and enthused about trying to identify photographs from various CRS chapters from around the world.
- Q What are the main benefits and rewards in volunteering for CRS?
- A Volunteering for CRS is a service, and it's a way of serving and progressing my discipline. So a reward is to see our international society continuing to progress and flourish and to be contributing to the advance of this science and technology through its annual conferences, workshops, symposia, publications (books and journals), and now our first webinars.

In addition, there are other personal rewards, a particularly important one being the international network that I have established through my volunteering role and activity on various CRS committees. I now have colleagues around the world with whom I enjoy interacting—catching up with and talking about not just science but also other things of personal interest.

Although it doesn't matter for me so much now given the stage of my career, for young volunteers an additional reward

comes of having their volunteering activities on their CVs, which is always good for promotion and job opportunities.

### ${f Q}$ How do you feel our society stands out from other organizations?

A Our society stands out in several ways. First, it is a truly international organisation with a global membership. I was particularly pleased to be able to support the establishment of a new chapter of CRS in Malaysia (MyCRS, a brilliant name for a chapter). When I was in China last year, I was also delighted to be able to meet with the current president of the CRS China Local Chapter and to help advance its activities in China.

Second, we stand out because we are a multidisciplinary organisation. CRS science and technology is essentially collaborative, and it requires that multidisciplinary approach involving polymer chemists, molecular biologists, pharmaceutical scientists, and animal health people. In



addition, the Consumer and **Diversified Products** (C&DP) section brings an additional richness to the organisation because there is crossfertilisation between the bioactives, C&DP, and preclinical sciences and animal health areas. As we work to build relationships with end users of our science and technology (diabetes specialists, ophthalmologists, and others) we add

On a swing bridge in New Zealand.

more richness to our organisation and contribute to the translation of our important science and technology and to products that will benefit patients.

### ${f Q}$ What is your advice for new members and volunteers in CRS?

A Before volunteering, talk to the chair of the committee involved or to experienced volunteers, and determine what the expectations of the position are. I believe it is important that once you have volunteered for the position you can contribute effectively and actively to that position. Our society will rise and fall on the activity and effectiveness of the volunteers. Once you've determined the time and work commitment and then made the decision to "go for it," I would encourage you to organise your life and priorities appropriately so that your contribution can be an active and beneficial one for the organisation. When you attend your meetings, make sure that you've read the background materials provided for the meetings, are aware of the agenda, and are ready and willing to contribute to the discussion with thoughtful and constructive ideas.

# Q Name one strategy you have used to facilitate a committee to work effectively.

A I think committees work effectively if they have clear understanding of what's being asked of them. Therefore, an agenda for a meeting is important, but it must also be an effective agenda. Background materials should be provided before the meeting so that people can come to the meeting informed for constructive and effective contributions. It's also important that agendas give the committee clear direction in what's required. For example, there is limited value in having an item on the agenda that says "to discuss..." Rather, it is better to have an item that says "to approve the...." Then the committee knows that its task is to consider the item and to decide whether or not to approve it. It's not being asked to go into a long-winded discussion with no decision being made at the end.

# Q Being president of CRS is a huge time commitment. Do you have advice about how to manage your job and CRS commitments?

A As I said earlier, before taking on a role in CRS, it's important to talk to people who know what is involved to get some understanding of the time commitment and effort required. Once this is understood, and if you agree to take on the role or stand for election in a particular role, then it's incumbent on you to manage your time and commitment appropriately. This means the usual types of techniques that are used—using your diary effectively, using your time effectively, and getting your priorities appropriately balanced. Of course, from time to time personal issues do arise, which means that good intentions of doing some tasks are sometimes not fulfilled. In my experience, other members of committees and the Board have been very understanding of this situation. They recognise that it's a volunteer organisation and that sometimes things will get in the way of someone meeting the commitments, and so they are able to move forward with good grace.

### And finally, a few rapid-fire questions to conclude.

Beach or mountains?	Beach.
Wine or beer?	Wine.
Plane or train?	Train.
Polymers or lipids?	Polymers.
Drugs or devices?	Drug-device combinations.
Soccer or cricket?	Cricket.

We thank Ian for taking time to share his valuable experience on volunteering. We take this opportunity to acknowledge the significant time, energy, and commitment that Ian has invested in our society. Under Ian's leadership CRS has grown and is well placed to attain the society's vision.

### CRS University of Missouri– Kansas City Student Chapter

### Vivek Agrahari, Chapter President

The new CRS Student Chapter of the University of Missouri– Kansas City was officially recognized in May 2015. The CRS-UMKC Student Chapter is a student organization providing a forum to interact with scientists, academics, and people in the industry and to communicate ideas and learn from them about the field of drug delivery systems and controlled release. As a student chapter, we are dedicated in the progression of delivery systems and controlled release technology and are willing to contribute toward the advancement of science.

### **Objectives and Goals**

- Increase student participation in the activities of CRS at the national and international levels.
- Increase student awareness of career opportunities in the pharmaceutical sciences.
- Increase student awareness of the latest advances and discoveries in the pharmaceutical sciences.
- Provide students in the pharmaceutical sciences with opportunities for professional advancement and leadership development.
- Foster participation in outreach activities that further the goals and objectives of CRS.

### **CRS-UMKC Student Chapter Officers**

President: Vivek Agrahari President-Elect: Vibhuti Agrahari Vice-President: Ashutosh Barve Treasurer: Mary Joseph Secretary: Abhirup Mandal Faculty Adviser: Dr. Russell B. Melchert Scientific Adviser: Dr. Ashim K. Mitra

### UKICRS Sponsors Summer Studentship Initiative

Gavin Andrews, Queen's University of Belfast, United Kingdom



At the CRS United Kingdom–Ireland Local Chapter (UKICRS) we are constantly asking ourselves how to best serve our members and make a meaningful contribution to education within the broad area of controlled

drug delivery. To this end, UKICRS announced a new UKICRS Summer Studentship award, which will provide funding for an undergraduate student to spend up to eight weeks during their summer vacation conducting independent research in the general area of controlled release and pharmaceutical sciences.

Information about the Summer Studentship award went live on the UKICRS website in late 2014 and was extremely well received. Many thanks to all applicants for their enthusiasm and efforts. Following internal review by the UKICRS committee, we were pleased to announce that this year's Summer Studentship had been awarded to Zhiyuan Kok, a third-year M.Pharm. student at the University of Nottingham who is extremely passionate about science and has already attended the Nobel Prize Ceremony in 2008, after winning a national science competition. Under the supervision of Giuseppe Mantovani, Zhiyuan will be conducting an eight-week project on the topic "Synthesis of Multivalent Glyco-polymers for Selective Lectin Targeting." Following completion of this exciting project, Zhiyuan will have the opportunity to write a short article describing the summer project for inclusion in the 2016 UKICRS newsletter.

As a committee, we are extremely excited about this new initiative because it provides a mechanism by which undergraduate students may learn about cutting-edge research in the company of other young budding scientists. Moreover, we are thrilled to offer students the opportunity work in an engaging and dynamic research team, conducting their own research while also learning about the work of others. We hope that this unique experience will not only be hugely fun and rewarding but, additionally, that it will stimulate enthusiasm for controlled drug delivery and science in general.

# **CRS Election Results**

The 2015 CRS election votes have been tallied and the results finalized. The nomination process, led by the Nominating Committee headed by Ian Tucker, allowed for many opportunities for member input. The newly elected Board of Directors and Board of Scientific Advisors, listed below, will begin their new positions on July 29, 2015, at the conclusion of the annual meeting. Thank you to all the impressive candidates who participated in this election. Thank you to all the members who voted this year, helping to shape the future of our society. For a complete list of Board of Directors and Board of Scientific Advisors members, see the CRS website.

Congratulations to our newly elected CRS Board



President-Elect **Ruth Schmid** SINTEF, Norway



Treasurer-Elect Christine Allen University of Toronto, Canada



Secretary **Ben Boyd** Monash University, Australia



Director-at-Large Justin Hanes Johns Hopkins University, U.S.A.



Director-at-Large Nicole Papen-Botterhuis TNO, the Netherlands

### **Board of Scientific Advisors**



Daniel Bar-Shalom University of Copenhagen, Denmark



Craig Bunt Lincoln University, New Zealand



Peter Cheifetz Merial Inc. (A Sanofi Co.), U.S.A.



Michael Doschak University of Alberta, Canada



Hideyoshi Harashima Hokkaido University, Japan



Arlene McDowell University of Otago, New Zealand



Arto Urtti University of Helsinki, Finland

In addition to the newly elected Board members listed above, the following CRS members are also serving on the 2015-2016 Board.

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

Immediate Past President Arthur Tipton Southern Research Institute, U.S.A. Treasurer Christopher McDaniel White Creek Pharma Advisors, U.S.A.

Director-at-Large Maria José Alonso University of Santiago de Compostela, Spain Director-at-Large Andrew Lewis Ipsen, France

Director-at-Large James Oxley Southwest Research Institute, U.S.A.

# **Greetings from Around the Globe**

### To capture the global appeal of CRS, our editors send you greetings!



Bo Michniak-Kohn on a chilly spring morning in New Jersey.

Chuck Frey considers the potential to shoot par, on at least one hole, in mid-May in southern Wisconsin.



Arlene McDowell explores the outdoors in Dunedin, New Zealand, "the Riviera of the Antarctic."

Rod Walker is



Steve Giannos sends greeting from Galveston, Texas.







# Welcome New CRS Members

Priyanka Agarwal Swati Agrawal Nicolas Alcaraz Jihad Alsaddique Christopher Baker Stephen M. Black Kaitlin Bratlie Javier Calles Rae Sung Chang Kuan-Ju Chen Injeong Choi José Crecente-Campo Fraser Crofts Richard D'Arcy David Dahlgren Ioe De Sousa Joke Devoldere Bernadette DSouza Ioanne Du Stella-Saphira Ehrenberger Signe Erickson James Essinger Yao Fu Gregor Fuhrmann Suniket Fulzele

Marcos Garcia Fuentes Feng Geng Tao Gong Mee Ree Han Li Hanmei Jeremiah J. Harnett Leila N. Hassani-Beniddir Kevin P. Herlihy Di Huang Sameer Joshi Martti Kaasalainen Manju Kanamala Limor Kaneti Hidemasa Katsumi Swapnil Khadke Hyungjin Kim Jiyeon Kim Kenji Kono Kristiina Korhonen Niklaus Künzle Kosuke Kusamori Frederic Lagarce Sua Lee Hansol Lee Hélène Lesbros

Lian Li Man Li Yanping Li Cristina Loira Pastoriza Dainius Macikenas Mohammed Mahdi Helene Malhaire ShengJun Mao Joanne McCaffrey Ian McIntosh Sankaranarayana Murugesan Ioanna Mylonaki Rong Ni Amaya Nino Cian O'Leary Jaclyn Obermeyer Jiwon Park Karen Peynshaert John Pollard Sonia Reimondez Carl Roos Charles Sanson John Sheehan Mayank Singhal Alejandro Sosnik

Peter Stone Stephan Stremersch Chia Yu Su Tong Sun Carolin Thiele Steliyan Tinkov Barbara M. Torrisi Uloma Ubani-Ukoma Warren Viricel Hsuan-Yao Wang Thomas Werfel Yongtao Wu Li Xie Mimi Yang Qingging Yang Muhammad Naveed Yasin Burcin Yavuz Eiji Yuba Peng Zhang Quan Zhang Ting Zhang Zhirong Zhang



From the Controlled Release Society and the American Association of Pharmaceutical Scientists

# Formulation, Processing, and Testing of Functionally Coated Multiparticulates Workshop

### October 24 • Orlando, Florida, U.S.A.

Held immediately prior to the AAPS Annual Meeting and Exposition

### This workshop will:

- Review the advantages of multiparticulate dosage forms in regard to dosing flexibility, i.e., targeted dosing and timed dosing.
- Provide firsthand, practical knowledge about formulation and process development of multiparticulate dosage forms—including beads, pellets, and mini-tablets.

### Workshop Organizers

Don Barbieri, Patheon, U.S.A. Lauren (Wood) Petraglia, LCI Corporation, U.S.A.

**Register today!** Visit **controlledreleasesociety.org** to register and view workshop details.



# **Patent Watch**

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

This article briefly summarizes novel aspects of selected U.S. patents involving controlled release or delivery that were issued from July 1 to December 31, 2014. Selections have been loosely categorized into interest areas; however, many overlap into other categories. Greater detail on each can be found on the U.S. patent website at http://patft.uspto.gov/.

### **Abuse Deterrent**

U.S. patent 8,921,418 – Controlled release of a phenolic opioid from a prodrug is achieved through intramolecular cyclization triggered by enzymatic activity.

U.S. patents 8,920,833 and 8,920,834 – A superabsorbent material such as polycarbophil is used to provide a swellable matrix that encapsulates and retards release of contained drug particles upon exposure to aqueous media.

U.S. patents 8,808,745 and 8,877,241 – A dosage form consisting of a conus-like shape is configured to control initial surface erosion and provide zero-order release of an opioid.

U.S. patent 8,871,265 – This invention involves an abuse deterrent, controlled release opioid formulation employing a gelling agent to impart a viscosity unsuitable for administration when crushed or mixed with water.

### Agriculture

U.S. patent 8,901,037 – Allyl isothiocyanate alone or in combination with other substances is applied in an immediate release or encapsulated controlled release format for germination prevention and weed control.

U.S. patent 8,888,887 – Release of a plant fertilizer core material is controlled with polyurethane/cross-linked wax coating compositions.

U.S. patent 8,801,827 – A controlled release boron fertilizer is prepared by incorporating a boron source in molten elemental sulfur.

U.S. patent 8,764,873 – Animal waste is used as a coating layer on typical fertilizer particles to control release of the fertilizer and coating nutrients.

#### **Biodegradable Systems**

U.S. patent 8,883,188 – Sustained bioactive release is achieved with modular biomedical supramolecular structures that can be resorbed through cell-mediated degradation, enzymatic degradation, and/or hydrolytic degradation.

U.S. patent 8,877,705 – This invention involves use of biopolymer networks in combination with enzymes for controlled release of active substances on surfaces in pharmaceutic or cosmetic applications.

#### Buccal

U.S. patent 8,865,198 - A periodontal insert for controlled

delivery of anti-inflammatory or antibacterial agents for four days to six weeks is disclosed.

U.S. patent 8,795,638 – Oral tissue-adherent salts that control release of biocidal ions are disclosed.

### Complexes

U.S. patents 8,871,269 and 8,900,636 – Sustained release of highly soluble bioactives with minimal degradation is achieved through ion pairing with organic pairing ions in a biodegradable polymer matrix.

### Eye

U.S. patents 8,821,457 and 8,894,602 – Implants with directional release for controlled bioactive delivery to the lacrimal fluid of the eye are described.

U.S. patent 8,877,229 – Particles consisting of biodegradable polymers and bioactive material are delivered intravitreously for sustained bioactive release for up to 6 months.

### Food

U.S. patent 8,889,654 – Glycogen is used as a source/means for controlled release of glucose in food formulations.

### **Household Products**

U.S. patent 8,888,924 – Controlled release detergent compositions with anti-depositional properties consisting of cellulosics, sugars or salts, and polycarboxylic acids are disclosed for fabric cleaning, dish cleaning, and the like.

### **Hydrogels**

U.S. patent 8,912,247 – Improved methods of preparing polyethylene glycol fumarate to create injectable hydrogels for controlled release of bioactives are disclosed.

U.S. patent 8,883,862 – A hyaluronic acid–based hydrogel is used to create an injectable formulation for controlled release of bioactive for treatment of osteoarthritis.

#### Implants

U.S. patent 8,784,373 – Carbon nanotube based devices are anchored to deliver drug over an extended time period.

### Liposomes

U.S. patent 8,877,242 – Liposomes are used in combination with biodegradable polymers to provide implantable compositions for controlled bioactive material release.

U.S. patent 8,808,733 – A photo-labile molecular cage is used to control release of an activator that subsequently induces bioactive agent release from a liposome.

### Manipulations

U.S. patent 8,882,747 – A magnetic field, an electric field, or electromagnetic signals are employed to control release or delivery of bioactive material to an environment such as the body of an organism, body of water, or enclosed reservoir.

U.S. patent 8,878,638 – This invention involves the use of magnetic conduits and magnetic domain walls to digitally move or position magnetic particles in microfluidic systems.

U.S. patent 8,768,501 – Magnetically actuated propellers sized from 20 nanometers to 100 microns are controlled by magnetic fields for various purposes including controlled drug or object delivery.

### Materials

U.S. patent 8,901,341 – A new class of hydrolysable amino acid derivatives and absorbable polyester amides, polyamides, polyepoxides, polyureas, and polyurethanes prepared from them are disclosed for drug delivery and a variety of medical uses.

U.S. patent 8,852,645 – Bioactive material is incorporated into controlled release toroidal-spiral shaped particles that are created during sedimentation of polymer solution droplets.

U.S. patent 8,846,853 – A direct polycondensation method is described for manufacture of high-purity medical biodegradable polylactic acid for controlled release applications.

U.S. patent 8,846,072 – Sustained release of anesthetic over 24 to 72 hours is controlled by the use of a sugar ester.

U.S. patent 8,828,415 – An alternative interfacial polymerization process that creates an acetylene carbamide–polyurea polymer coating for agrochemicals, pharmaceuticals, catalysts, phase transfer materials, and the like is disclosed.

### Miscellaneous

U.S. patent 8,916,198 – Enhanced surface area on acid-modified wollastonite particles is used for controlled release of proteins.

U.S. patent 8,888,732 – An intraluminal sleeve for controlled active agent release to the intestine is disclosed for treating obesity.

U.S. patents 8,883,201 and 8,883,203 – Medium-chain fatty acids or their derivatives are employed for enhanced intestinal bisphosphonate uptake in the treatment of osteoporosis.

U.S. patent 8,865,205 – A swellable polymeric coating on sutures provides controlled delivery of bioactive agents with antimicrobial, anti-inflammatory, anesthetic, tissue growth promoting, or antineoplastic activity.

U.S. patent 8,846,100 – A multiparticulate strategy for pulsed delivery of amphetamine salts is disclosed for capsules, tablets, or sachets.

U.S. patent 8,840,951 – This invention relates to preparation of controlled release systems consisting of drug covalently bound in polymeric carriers or devices such as micelles or nanoparticles.

U.S. patent 8,821,928 – A layered, cylindrical oral pharmaceutical composition designed to release a bioactive throughout the stomach and intestinal regions is disclosed.

U.S. patent 8,808,752 – Hydrophobic antibiotic compounds are dissolved in hydrophobic vinyl monomer without solvent to produce a controlled release antibiotic upon polymerization.

U.S. patent 8,765,178 – A pharmaceutical tablet consisting of a first layer containing one active agent between two adjacent controlled release layers containing at least one second active agent is described for controlled release of each active agent.

U.S. patent 8,765,177 – A bioadhesive composition tablet is formulated for extended buccal, vaginal, nasal, or rectal delivery.

### **Nasal Delivery**

U.S. patent 8,877,230 – An intranasal gel for sustained release of testosterone is disclosed.

### **Osmotic Systems**

U.S. patent 8,920,835 – An osmotic tablet consisting of a drug layer, a push layer, a membrane between the drug and push layer, and rigid semipermeable outer layer is used to achieve constant drug release following the initial early release rates.

U.S. patent 8,920,654 – Composite thin-film membranes consisting of two or more layers are described for forward and pressure retarded osmosis applications such as industrial product or waste concentration, hydration bags, energy or pressure generation, or controlled drug delivery.

### **Personal Care**

U.S. patent 8,834,857 – A low-solubility deodorizing salt is used to extend release based on solubility.

### **Recognitive Release Systems**

U.S. patent 8,846,103 – Cross-linked materials containing multivalent cross-linking agents are used to provide insulin release in response to the presence of saccharide molecules.

U.S. patents 8,771,713 and 8,821,899 – This invention involves imprinted or recognitive polymers for controlled delivery of an active agent in response to a molecular binding that upsets the structural integrity of the polymers.

### **Transdermal**

U.S. patent 8,916,191 – An acrylic polymer matrix patch system for transdermal controlled delivery of methylphenidate and the like is described.

U.S. patent 8,834,447 – Nano-particles that absorb in the near-IR region are incorporated into transdermal systems to allow use of near IR radiation to heat the particles and deliver formulation bioactives in a controlled manner.

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# In the News

Compiled by Steven Giannos, Independent Consultant

### May

# Eli Lilly and Company Reveals Plan for Innovation Center in Cambridge, Massachusetts

PRNewswire: May 6, 2015 – INDIANAPOLIS, IN, U.S.A. – Eli Lilly and Company (NYSE: LLY) today announced plans to establish a new drug delivery and device innovation center in Cambridge, Massachusetts—a strategic location that will help attract top scientists and bioengineers, as well as enhance Lilly's local business development presence.

The Lilly Cambridge Innovation Center, a makerspace located in Kendall Square, will allow leading life science experts and organizations to explore how emerging technologies and connectivity can advance drug delivery and device innovation to improve patient health.

Lilly chairman, president, and CEO John C. Lechleiter, Ph.D., said the company is locating a portion of its delivery and device organization in Cambridge—one of the nation's leading regions for research and development of medical delivery technologies to take advantage of the area's rich engineering talent base and life sciences ecosystem.

"The Lilly Cambridge Innovation Center complements a deliberate push by the company to be an industry leader in providing convenient, reliable drug delivery and device innovation," Lechleiter said. "Locating in Cambridge is an important strategic move for achieving this goal, as it provides us access to a concentration of high-caliber academic institutions, cutting-edge life science and technology companies, and some of the world's leading talent."

Lechleiter added that the center will serve as a portal for external partnerships and collaboration activities with the company's existing research facilities in San Diego, New York City, and Indianapolis.

Construction of the Lilly Cambridge Innovation Center will begin immediately, with an expected occupancy by the end of 2015. Over the next two years, the company will hire about 30 scientists and engineers to fulfill the center's work. When fully operational, the center will increase the company's delivery and device research and development space by nearly 50%, while increasing its staff by 25%.

The investment in Cambridge, part of the company's planned growth strategy in research and development of drug delivery and device technologies, "underscores Lilly's commitment to providing meaningful innovation in this arena," said Jan Lundberg, Ph.D., executive vice president of science and technology and president of Lilly Research Laboratories. Lundberg added, "New drug delivery and device innovation is critically important to Lilly's growing portfolio of potential medicines, particularly in our focus areas of diabetes, neurodegeneration, immunology, and pain. The best therapies of the future will marry breakthrough scientific discovery with customer-friendly devices. That's what will make life better for people who need our medicines and give Lilly a true competitive edge."

Lilly's drug portfolio and pipeline have changed significantly over the past decade. More than half of the company's pipeline now comprises biologics that require some type of injection. The company expects its revenues from device-enabled products to double by 2020.

### **Mati Therapeutics Expands Patent Portfolio**

Business Wire: May 6, 2015 – AUSTIN, TX, U.S.A. – Mati Therapeutics Inc. ("Mati") announced today that it has been granted U.S. patent number 9,011,361 entitled "Lacrimal Implant Detection" and European Union patent number EP2614844 entitled "Drug Cores for Sustained Release of Therapeutic Agents." These patents provide coverage for important elements of Mati's novel punctal plug delivery system (PPDS) for treatment of ocular indications including certain features for detecting the implants in the puncta and in the composition of the drug-eluting cores that feature in this technology.

Mati's current IP portfolio includes 15 patent families that span the PPDS platform and related product candidates. At present, a total of 57 patents have been granted or allowed and an additional 98 patents are pending. These granted and pending patents cover major national and international markets, including the United States, Europe, Japan, Canada, Korea, Israel, China, Hong Kong, Singapore, Russia, Taiwan, Brazil, Mexico, and India. The earliest filed PPDS platform technology patent family has a projected expiry date in 2027, with other families projected to expire at different times through 2033.

"In the past year an additional 17 patents have been granted or allowed, further bolstering our growing intellectual property portfolio for Mati's PPDS technology," commented Bob Butchofsky, CEO of Mati. "We believe the PPDS platform technology may potentially be used to treat several ocular indications, including glaucoma, post-cataract surgery, ocular allergies, and dry eye disease, each representing potentially substantial market opportunities for Mati."

Mati continues to develop, support, and maintain its intellectual property portfolio with the goal of providing protection from competitors and further expanding the patent coverage for the PPDS platform. While the protection afforded by intellectual

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property is subject to uncertainties, Mati believes that its patent portfolio provides meaningful protection for the PPDS delivery platform.

Mati's current focus is on the latanoprost punctal plug delivery system (L-PPDS) for patients with ocular hypertension and glaucoma. The program is currently in a phase IIb multi-center clinical trial in the United States.

Mati is developing PPDS, a sustained release ocular drug delivery platform that Mati believes has the potential to treat a range of ocular indications. The platform utilizes a device called a punctal plug, which is inserted into a patient's tear duct (or punctum). The device is already approved to treat dry eye syndrome, but Mati is the first to conduct clinical trials in the United States testing punctal plugs as an anchoring device for a drug delivery platform. A drug-eluting core is inserted into Mati's proprietary punctal plug, which allows medication to be continuously released into the tear film of the eye over a period of time. Mati believes PPDS has the potential to become a more reliable alternative to several eye drop therapies, which can be ineffective because many patients are unwilling or unable to adhere to self-administered eye-drop regimens.

L-PPDS is the first product candidate that Mati is seeking to develop and commercialize using the PPDS platform. L-PPDS utilizes a drug eluting core containing latanoprost, which is currently used as an eye drop medication to treat elevated intraocular pressure in patients suffering from ocular hypertension and open-angle glaucoma. Since acquiring the PPDS development program from QLT Inc. in April 2013, Mati has designed and initiated a final phase IIb trial of L-PPDS. If the results of the phase IIb trial are favorable, Mati intends to use the results to finalize a protocol for a phase III pivotal trial of L-PPDS. There can be no assurance that Mati will apply for or secure the regulatory approvals needed to sell L-PPDS or any other product using PPDS or as to whether commercially viable markets will exist for any approved product.

Mati was founded by former senior officers of QLT Inc., including Bob Butchofsky, CEO of Mati and former CEO of QLT Inc., and Chris Muller, former head of cornea, refractive, and medical marketing at Abbott Medical Optics. Combined, the senior management team of Mati has over 75 years of ocular development and commercial experience. Mati's corporate head office is in Austin, Texas. Mati undertakes research and development activities through its wholly owned Canadian subsidiary, Mati Therapeutics (Canada) Inc.

### Pernix Releases Pharmacokinetic Data for ZX007

Business Wire: May 5, 2015 – MORRISTOWN, NJ, U.S.A. – Pernix Therapeutics Holdings, Inc. (NASDAQ: PTX), a specialty pharmaceutical company, today announced the successful completion of a human pharmacokinetic equivalence study with ZX007, an innovative abuse deterrent tablet formulation of hydrocodone bitartrate. The clinical study evaluated the pharmacokinetics and safety of prototype formulations developed by Altus Formulation using its proprietary INTELLITAB<sup>™</sup> technology, for comparison with Zohydro<sup>®</sup> ER, resulting in the selection of the final ZX007 prototype for pivotal clinical studies. Damon Smith, CEO of Altus Formulation, said, "We are very happy that ZX007 is performing in the way we expected in human studies and we look forward to working with the Pernix team to complete development."

Study results demonstrated that the selected ZX007 formulation is pharmacokinetically equivalent with currently marketed Zohydro ER with BeadTek and that it has a consistent safety profile. Selection of the formulation enables the start of pivotal clinical studies later this year, paving the way for the NDA submission for ZX007 in mid-2016. Doug Drysdale, president, chairman, and CEO of Pernix, said, "We are pleased to have identified the right formulation to move forward into clinical trials, to bring the clinical benefits of ZX007 to patients suffering with chronic pain. Pernix remains committed to supporting the appropriate use of opioids, which includes following best practices for physicians and their patients living with chronic pain, as well as making abuse-deterrent products available."

The Zohydro ER NDA and related investigational new drug applications were transferred from Zogenix to Pernix immediately upon closing on April 24, 2015, and Pernix has assumed regulatory and financial responsibility for the ongoing efforts related the development of ZX007, with Zogenix providing assistance in the clinical development of the program under a transitional services agreement for up to 18 months.

### April

### Bonesupport Announces CE Mark of Cerament™|V, the First Injectable Vancomycin-Eluting Bone Substitute in the Management of Osteomyelitis

PRNewswire: April 29, 2015 - LUND, Sweden - Bonesupport, an emerging leader in injectable bone substitutes for orthopedic trauma, bone infections, and instrument augmentation related to orthopedic surgery, announced that it has received CE mark for Cerament<sup>™</sup> |V, the first injectable vancomycin-eluting bone substitute indicated to promote and protect bone healing in the management of osteomyelitis. Cerament<sup>TM</sup>|V is an extension of the company's antibiotic-eluting bone substitute portfolio, which includes Cerament<sup>™</sup>|G, the first injectable gentamicin-eluting bone substitute. Vancomycin is used to treat gram-positive bacteria that are known to be resistant to most antibiotics, including methicillin-resistant Staphylococcus aureus (MRSA). The Infectious Disease Society of America recommends vancomycin as first-line therapy for these complicated infections, which include bone and joint infections. The company is launching Cerament<sup>™</sup> | V immediately in all CE mark countries.

"Antibiotic-resistant infections are among the most challenging clinical conditions to manage," said Pablo S. Corona, M.D., Ph.D., from the Reconstructive and Septic Surgery Division,

### GLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOB

In the News continued from page 27

Department of Orthopaedic Surgery, Hospital de Traumatologia y Rehabilitacion Vall d'Hebron, Barcelona, Spain. "Local, highdose antibiotic delivery is particularly effective in managing and preventing infections, as seen with Cerament<sup>™</sup>|G. Now with the availability of Cerament<sup>™</sup>|V, surgeons have two powerful weapons that address the most common bacteria in the fight against osteomyelitis."

Cerament<sup>TM</sup> | V is an injectable, resorbable bone graft substitute that remodels into healthy native bone within 6–12 months and is designed to fill bone gaps and voids and can augment hardware and bone fractures during surgical procedures. The efficient elution profile and the focused local delivery of vancomycin obtained with Cerament<sup>TM</sup> | V is intended to prevent colonization of sensitive microorganisms, thereby protecting the bone healing, particularly in challenging cases of deep bone infection.

"Expanding our portfolio of drug-delivery therapeutics is an important part of our growth strategy, and we are proud to be executing on that with the launch of Cerament<sup>TM</sup>|V," said Lloyd Diamond, CEO of Bonesupport. "As a pioneer of antibioticeluting bone substitute technology, the launch of Cerament<sup>TM</sup>|V marks the first ever injectable bone substitute with two drugs, vancomycin and iohexol, to receive approval. This is an important milestone because it paves the way for future drug delivery combinations using our propriety technology and the Cerament<sup>TM</sup> platform."

Osteomyelitis, or bone infection, is a \$1.7 billion market where prolonged, long-term antibiotic therapy, multiple surgical interventions, and the threat of amputation are the current standard of care. Rising prosthetic infections, diabetic ulcers, war injuries, sports injuries, and an increasing resistance to antibiotics contribute to this growing condition.

Bonesupport is an emerging leader of injectable bone graft substitutes for orthopedics, and trauma focusing on bone infection, instrument augmentation, and spinal applications. Cerament<sup>™</sup> is an injectable, synthetic bone substitute that mimics the properties of cancellous bone, allows for controlled resorption to support future bone ingrowth, and is injectable under local anesthesia for minimally invasive surgery. Cerament<sup>™</sup>|G and Cerament<sup>™</sup>|V are the first CE-marked injectable antibiotic-eluting ceramic bone graft substitutes indicated to promote and protect bone healing in the management of osteomyelitis, (bone infections). Cerament's unique biologic properties deliver a consistent, prepacked, and ready-to-use formulation to facilitate optimal delivery. Cerament<sup>™</sup>|G and Cerament<sup>™</sup>|V are not available in the United States.

Cerament<sup>™</sup> is a fully developed product platform that is commercially available in the United States, Europe, Southeast Asia, and the Middle East. Cerament<sup>™</sup> is revolutionizing the treatment of fragility and other fractures caused by disease and trauma. Scientific research of Cerament spans more than 11 years. Over 45 preclinical, clinical, and animal studies have been conducted and more than 10,000 patients have been treated with Cerament. The company was founded in 1999 and is based in Lund, Sweden, with subsidiary locations in the United States and Germany. To learn more about Bonesupport, please visit www.bonesupport.com.

### Orexo: New 24-Week Clinical Study Strengthens the Evidence of the Therapeutic Value of Zubsolv® for Maintenance Treatment of Opioid Dependence

Business Wire: April 22, 2015 – UPPSALA, Sweden – Orexo AB (STO: ORX) today announced data from a 24-week clinical trial assessing the long-term safety and efficacy of Zubsolv<sup>®</sup> (buprenorphine/naloxone) sublingual tablet (CIII) for the maintenance treatment of opioid dependence. The results establish that Zubsolv is effective, well tolerated, and demonstrated a safety profile consistent with the product labeling for sublingual buprenorphine products. In addition, less than 1% of the patients exited the study due to treatment failure, which further underpins the medical value of Zubsolv. The results also demonstrated an increase of 15% in employment by the patients participating in the study, which further strengthen the evidence of the value of effective treatment of opioid dependence for society.

"This study reinforces and further highlights the safety and effectiveness of Zubsolv. Over the course of six months, the safety profile of Zubsolv was consistent with previous buprenorphine studies, and patient symptoms continued to improve. In addition, we were able to observe the benefits of long-term treatment with Zubsolv on work productivity. As patients continued on their path to recovery, they experienced positive gains for employment status, hours of work missed, number of hours patients were able to work, productivity, and impairment of daily activities," said Michael Sumner, chief medical officer of Orexo.

The primary objective of study OX219-008 was to assess the safety and tolerability of Zubsolv after an additional 24 weeks of treatment. The results from study OX219-008, a multicenter, open-label, 24-week follow-up study (N = 665), establish that Zubsolv is well tolerated and effective for opioid-dependent patients following six months of treatment. The safety profile was consistent with the product labeling for sublingual buprenorphine products.

The most common adverse effect was constipation (2.9%), and no individual events were reported in  $\geq$ 5% of patients. There was one serious adverse event (SAE) that was considered treatmentrelated (depression that started on day 19 and ceased on day 27), and six patients discontinued the study with AEs that were considered by the investigator to be possibly related to treatment.

Retention rates at week 24 (end of study) were consistent with previous long-term clinical trials with buprenorphine. The retention rates at weeks 4, 8, 12, 16, 20, and 24 (EOS) were 84.7, 72.6, 63.9, 57.6, 50.1, and 43.9%, respectively. Opioid cravings were assessed on a 100 point VAS where 0 represented "no

### EGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLO

cravings" and 100 represented "the most intensive craving" the patient had ever had. Craving scores continued to improve during the extension study. At baseline of the parent studies before treatment was initiated, the mean opioid craving score was 70.8 and, by week 24, the mean score had been improved to 10.9 in patients who completed the study.

Health economic outcomes were assessed using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem assessment (WPAI: SHP). The WPAI: SHP assessed seven items related to work productivity and impairment associated with opioid dependence. By the end of the study in week 24, 15% more patients were currently employed compared with the parent study baseline. In addition, patients reported missing 4.8 fewer hours of work per week on average due to their opioid dependence. Mean hours actually worked per week increased by 4.6 hours per week from baseline. Patients also reported improvements in the degree to which their opioid dependence affected their productivity and daily activities.

Study OX219-008 was an extension of the ISTART (study 006) and study 007. Results from both of the parent studies have previously been released and can be found under the following link (www.orexo.com/en/investor-relations/press-releases/?guid=899375). The ISTART study showed Zubsolv was as effective as Suboxone<sup>®</sup> film, and more than 70% preferred Zubsolv after being exposed to both Zubsolv and Suboxone film.

"The results of this extension study represent another addition to the already robust evidence base supporting Zubsolv as an effective and well-tolerated maintenance treatment for patients struggling with opioid dependence. Zubsolv treatment supports opioid-addicted patients in gaining control over their life and improves their ability to function in society, as evidenced by the higher employment rates at the end of the observation period concurrent with the demonstrated reduction in opioid cravings. Orexo's investments in this follow-up study, and in planned future studies, demonstrate our continued commitment to advancing the treatment of opioid dependence for the patients suffering from this disease and providing effective and welltolerated therapies for physicians who treat them," said Nikolaj Sørensen, chief executive officer of Orexo.

### BIND Therapeutics Presents Data Highlighting Ability of Accurins to Control Biodistribution and Accumulate in Target Tissue at AACR Annual Meeting 2015

Business Wire: April 22, 2015 – CAMBRIDGE, MA, U.S.A. – BIND Therapeutics, Inc. (NASDAQ: BIND), a clinical-stage nanomedicine platform company developing targeted and programmable therapeutics called Accurins<sup>™</sup>, today announced that clinical and preclinical data from its oncology pipeline, including proprietary and collaboration programs, were presented at the American Association of Cancer Research (AACR) Annual Meeting 2015. The presentations include data from the company's lead proprietary Accurin drug candidate, BIND-014, and the Accurin drug candidate AZD2811, which is being developed in collaboration with AstraZeneca. "Collectively, these data demonstrate the unique attributes of Accurins as a new therapeutic modality and their potential to produce therapeutics with a best-in-class profile," said Andrew Hirsch, president and chief executive officer of BIND. "The data describing optimized pharmacological properties across a range of key therapeutic parameters for our proprietary product candidate, BIND-014, and AZD2811, our Aurora B kinase inhibitor program with AstraZeneca, demonstrate the ability of Accurins to control biodistribution and accumulate in target tissue across a broad spectrum of therapeutic payloads."

In a poster presentation entitled "Pharmacokinetics of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension) in Preclinical Species and Patients with Advanced Solid Tumors," BIND Therapeutics researchers presented clinical and preclinical data demonstrating that the Accurin BIND-014 provided prolonged circulation and controlled release of encapsulated docetaxel compared with conventional docetaxel consistently across multiple species. The controlled biodistribution and potential for targeted and preferential tumor accumulation may result in increased efficacy and decreased toxicity with BIND-014.

- BIND-014 preclinical and clinical pharmacokinetics (PK) demonstrated monophasic plasma concentration-time profiles well differentiated from solvent-based docetaxel.
- The Accurin BIND-014 displayed higher peak plasma concentration (Cmax) and area under the curve (AUC) with reduced clearance (CL) and volume of distribution (V<sub>d</sub>) for total docetaxel compared to solvent-based docetaxel.
- In all species, the  $V_d$  of BIND-014 was close to the blood volume. Cmax and AUC in human patients with solid tumors demonstrated dose linearity with an  $R^2$  of  $\ge 0.98$ ; repeat dosing did not have a significant effect on Cmax.
- Evaluation of encapsulated docetaxel plasma concentrations in patients and cynomolgus monkeys demonstrated that most circulating docetaxel was encapsulated in nanoparticles.

In a poster presentation entitled "Accurin-AZD1152 hQPA Nanoparticles Inhibit Growth of Diffuse Large B-cell Lymphomas and Small Cell Lung Cancer in Preclinical Models," data were presented demonstrating that the Accurin nanoparticle AZD2811 (formerly designated AZD1152-hQPA) exhibits promising *in vivo* and *in vitro* tumor growth inhibition as monotherapy in diffuse large B-cell lymphomas (DLBCL) and small cell lung cancer (SCLC). Time and duration of exposure are important, and these data also indicate that the Accurin nanoparticle AZD2811 has the flexibility to be delivered with different doses and schedules, offering the potential to adapt the therapeutic regimen to different tumors while achieving an improved therapeutic index.

• Models of DLBCL and SCLC show sensitivity to monotherapy Aurora B kinase inhibitors and AZD2811, with increased time of exposure resulting in greater cell death.

### GLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOB

In the News continued from page 29

- *In vivo*, Accurin nanoparticle AZD2811 inhibited tumor growth or resulted in tumor regression in multiple DLBCL and SCLC models.
- At 25 mg/kg dosed on day 1 and 3, Accurin nanoparticle AZD2811 provided either equivalent or superior activity to AZD1152 delivered at 25 mg/kg on days 1, 2, 3, and 4.
- Increased dose intensity resulted in increased antitumor effect, while modifying the timing and dose intensity of each dose cycle also influenced the antitumor activity.

In a poster entitled "Imaging Accurin-AZD1152 hQPA Nanoparticle Accumulation in Preclinical Tumours," data were presented that show the Accurin nanoparticle AZD2811 accumulates in tumors and achieves prolonged tumor drug exposure. This is the first time distribution of nanoparticles in tumors has been demonstrated.

- Imaging mass spectrometry analysis demonstrated that Accurin nanoparticle AZD2811 accumulates in preclinical tumor models and confirmed that the Accurin accesses the tumor and provides prolonged drug exposure and retention in the target tissue.
- Multiple imaging techniques demonstrated Accurin nanoparticle AZD2811 is still detected at nine days after nanoparticle administration, while no drug was detected 24 hours after the prodrug AZD1152 was administered.

Accurins are BIND's targeted and programmable therapeutics, which are designed, utilizing BIND's medicinal nanoengineering platform, with specified physical and chemical characteristics to target specific cells or tissues and concentrate a therapeutic payload at the site of disease to enhance efficacy while minimizing adverse effects on healthy tissues. Accurins are polymeric nanoparticles that incorporate a therapeutic payload and are designed to have prolonged circulation within the bloodstream, enable targeting of the diseased tissue or cells, and provide for the controlled and timely release of the therapeutic payload. BIND has demonstrated in preclinical studies that Accurins can improve tumor growth suppression, achieve higher concentrations of the payload in tumors compared with the payload administered in conventional form, and have pharmacokinetics and tolerability differentiated from their therapeutic payloads.

BIND Therapeutics is a clinical-stage nanomedicine platform company developing a pipeline of Accurins, its novel targeted therapeutics designed to increase the concentration and duration of therapeutic payloads at disease sites while reducing exposure to healthy tissue. BIND is leveraging its medicinal nanoengineering platform to develop a pipeline of Accurins targeting hematological and solid tumors and has a number of strategic collaborations with biopharmaceutical companies to develop Accurins in areas of high unmet need. BIND's lead drug candidate, BIND-014, is a prostate-specific membrane antigen (PSMA)-targeted Accurin that contains docetaxel, a clinically validated and widely used cancer chemotherapy drug. BIND-014 is currently in development for the treatment of non-small cell lung cancer, or NSCLC, in patients with KRAS mutations or squamous histology. In addition, BIND plans to initiate clinical trials with BIND-014 in cervical, bladder, head and neck, and cholangio cancers in 2015. BIND is also advancing BIND-510, its second PSMA-targeted Accurin drug candidate containing vincristine, a potent microtubule inhibitor with dose-limiting peripheral neuropathy in its conventional form, through important preclinical studies to position it for an Investigational New Drug (IND) application filing with the U.S. Food and Drug Administration (FDA) in 2016. Lastly, BIND is developing Accurins designed to inhibit PLK1 and KSP, both of which BIND believes are promising antimitotic targets that have been limited in the clinic due to myelotoxicity prior to reaching therapeutic doses.

BIND has announced ongoing collaborations with Pfizer Inc., AstraZeneca AB, F. Hoffmann-La Roche Ltd., and Merck & Co., or Merck (known as MSD outside the United States and Canada), to develop Accurins based on their proprietary therapeutic payloads and targeting ligands.

### Icon Bioscience Announces Pivotal Phase 3 Clinical Data Demonstrates Exceptional Efficacy of IBI-10090 in Reducing Inflammation Associated with Cataract Surgery

Business Wire: April 20, 2015 – SUNNYVALE, CA, U.S.A. – Icon Bioscience Inc., a specialty biopharmaceutical company focused on utilizing its patented and proprietary Verisome<sup>®</sup> extended-release drug delivery platform to develop unique intraocular eye-care therapeutics, today reported data from its pivotal phase 3 clinical trial for IBI-10090. The results of the trial showed that IBI-10090 is highly effective in treating inflammation post cataract surgery.

An estimated 4 million cataract surgeries are performed in the United States annually. Inflammation is common following such surgery and can lead to serious complications, if left untreated. Postoperative care typically involves the use of an ophthalmic anti-inflammatory medication applied topically several times daily over an extended period of time.

IBI-10090 employs Icon's Verisome® technology to dispense an extended-release, biodegradable formulation of the antiinflammatory agent dexamethasone into the anterior chamber of the eye through a single administration immediately following cataract surgery. "This is a novel therapeutic designed to improve the management of postsurgery inflammation," noted David S. Tierney, M.D., Icon's president and CEO. "IBI-10090 has been developed to increase efficacy by placing the drug at the site of action and to help patients, in a largely elderly population, avoid noncompliance and dosing errors associated with the comparatively burdensome process of multiple, self-administered, daily eye drops."

A discussion of the phase 3 results was presented on April 19 at the 2015 Annual ASCRS-ASOA Symposium & Congress by Eric D. Donnenfeld, M.D., clinical professor of ophthalmology, New York University and trustee, Dartmouth Medical School for the study investigators. Commenting on today's press release, Dr. Donnenfeld noted, "In this phase 3 trial, IBI-10090 showed

# EGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLO

unprecedented efficacy in reducing inflammation associated with cataract surgery, with a safety profile similar to that of placebo. IBI-10090 could prove to be an important new therapy as an alternative to frequent corticosteroid drop instillation in post cataract surgical care."

Vernon Wong, M.D., Icon's chairman and founder, said, "The success we have achieved to date with the development of IBI-10090 reflects the dedication and hard work of the entire team at Icon, and we are encouraged and excited about pursuing the next steps in bringing our first Verisome<sup>®</sup> based product out of the pipeline and into the marketplace."

# Envisia Therapeutics to Present at the Ophthalmology Innovation Summit

Business Wire: April 15, 2015 – RESEARCH TRIANGLE PARK, NC, U.S.A. – Envisia Therapeutics today announced that Dr. Benjamin Yerxa, president and cofounder, will present and participate in a panel discussion at the Ophthalmology Innovation Summit (OIS) being held in conjunction with the American Society of Cataract and Refractive Surgery (ASCRS) Annual meeting. OIS@ASCRS, as it is called, will take place on Thursday, April 16, 2015, at the Hilton San Diego Bayfront Hotel in San Diego, CA. The OIS was created to facilitate meaningful interactions and business partnerships between physicians, entrepreneurs, investors, and industry executives who are driving ophthalmic innovation.

Dr. Yerxa will highlight the company's PRINT<sup>®</sup> (Particle Replication In Nonwetting Templates) technology for the development of ocular therapies, as well as participate in a panel discussion during a special session titled Spotlight on Drug Delivery that takes place from 2:10 to 2:50 p.m.

Envisia uses the power of the proprietary PRINT technology to create particle-based ocular therapeutics that can deliver both small and large molecules in multiple formats. In February, the company announced the initiation of a phase 2a clinical trial to investigate the safety and tolerability of its lead product, ENV-515, in patients with glaucoma. ENV515 is an implantable, extended-release formulation of a marketed prostaglandin analogue that has the potential to offer glaucoma patients a therapeutic option that can sustain the reduction of intraocular pressure (IOP) over many months. Results are expected in mid-2015.

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

### Dicerna Presents New β-Catenin Data from Multiple Tumor Models at the 2015 RNA & Oligonucleotide Therapeutics Meeting at Cold Spring Harbor Laboratory

Business Wire: April 10, 2015 – CAMBRIDGE, MA, U.S.A. – Dicerna Pharmaceuticals, Inc. (NASDAQ: DRNA), a leader in the development of RNAi therapeutics, today announced promising new *in vivo* data for CTNNB1 DsiRNA in multiple patientderived xenograft (PDX) and other models of diverse tumor types. CTNNB1 DsiRNA is an extended Dicer substrate short interfering RNA (DsiRNA-EX) therapeutic targeting  $\beta$ -catenin delivered using Dicerna's proprietary next generation EnCore<sup>TM</sup> lipid nanoparticle (LNP) technology.  $\beta$ -Catenin, encoded by the CTNNB1 gene, is a well-studied oncology target that is validated by human genetic and functional evidence in a variety of cancers, including hepatocellular carcinoma (HCC), colorectal carcinoma (CRC), and intrahepatic cholangiocarcinoma (IHCC).

The data are being presented at the 2015 RNA & Oligonucleotide Therapeutics Meeting at Cold Spring Harbor Laboratory, held April 8–11, 2015, in Cold Spring Harbor, N.Y. The findings will be presented today in an oral presentation titled "Advances in Delivery of Dicer Substrate siRNAs (DsiRNAs) to Tumors" and were also presented yesterday in a poster presentation titled "Delivery of Dicer-Substrate siRNAs (DsiRNAs) to Patient-Derived Xenograft Tumors."

The findings demonstrate CTNNB1 DsiRNA's favorable pharmacokinetic (PK) and biodistribution properties as well as robust messenger RNA (mRNA) knockdown and tumor exposure in models of HCC, CRC, melanoma, leukemia, genetic hepatoblastoma, and other tumor types including PDX models.

"Dicerna's second generation EnCore LNP system has been further refined and is more broadly active than the first generation EnCore technology," said Douglas M. Fambrough, Ph.D., chief executive officer of Dicerna. "As a result, Dicerna is now able to show consistent gene knock down in an even wider range of tumor types, greater efficiency of tumor delivery, and delivery to both subcutaneous and orthotopic tumors. These findings provide us with a deeper understanding of the parameters that drive EnCore mediated tumor delivery and will help to inform our clinical development strategy as we move forward."

In an orthotopic HCC PDX model, a single dose of CTNNB1 DsiRNA yielded up to 90% knockdown of CTNNB1 and downstream effectors. Furthermore, Dicerna scientists observed rapid dampening of Wnt signaling in the tumor cells, but not in the adjacent normal liver tissue.

In addition to the HCC findings, Dicerna showed mRNA knockdown in models of hepatoblastoma, melanoma, leukemia, and CRC, providing further insights into the efficacy and delivery of EnCore mediated CTNNB1 DsiRNA in other tumor types. In one example, CTNNB1 DsiRNA delivery resulted in robust tumor growth inhibition in  $\beta$ -catenin-dependent CRC tumors.

### GLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOB

In the News continued from page 31

Dicerna continues to advance its EnCore LNP platform through extensive structure-function analyses to identify advanced formulation components and manufacturing processes. These advances have yielded a greater mechanistic understanding of tumor delivery, improved potency, and up to 10-fold improvements in tumor-specific delivery.

RNA interference (RNAi) is a highly potent and specific mechanism for regulating the activity of a targeted gene. In this biological process, certain double-stranded RNA molecules known as short interfering RNAs (siRNAs) bind to complementary messenger RNAs (mRNAs) and recruit proteins that break the chemical bonds that hold mRNAs together, preventing the mRNAs from transmitting their protein-building instructions.

RNAi therapeutics have the potential to treat a number of human diseases by "silencing" disease-causing genes. The discoverers of RNAi, a gene silencing mechanism used by all cells, were awarded the 2006 Nobel Prize for Physiology or Medicine.

Dicerna's proprietary RNAi molecules are known as Dicer substrates, or DsiRNAs, so called because they are processed by the Dicer enzyme, which is the initiation point for RNAi in the human cell cytoplasm. Dicerna's discovery approach is believed to maximize RNAi potency because the DsiRNAs are structured to be ideal for processing by Dicer. Dicer processing enables the preferential use of the correct RNA strand of the DsiRNA, which may increase the efficacy of the RNAi mechanism, as well as the potency of the DsiRNA molecules relative to other molecules used to induce RNAi. Dicerna's DsiRNA Extended (DsiRNA-EX) molecules resemble DsiRNA molecules but have an extended region at one end of the molecule that is engineered to provide additional functionality to the DsiRNA-EX molecules. Dicerna can also use this extended region to generate its DsiRNA-EX-conjugates, where a drug delivery agent is linked directly to the extended region of the DsiRNA-EX molecule, enabling the ability to deliver DsiRNA-EX conjugates to patients through a subcutaneous injection.

### Particle Sciences Receives Patent for Its Surface Arrayed Therapeutics™ Drug Delivery Platform

PRNewswire: April 6, 2015 - BETHLEHEM, PA, U.S.A. -Particle Sciences, a leading drug delivery CDMO, has received a Notice of Allowance for composition and use of the technology incorporated into its SATx<sup>™</sup> platform. The SATx<sup>™</sup> platform covers several structures that combine nanoparticles with surface bound large molecules. The technology has utility in applications ranging from oncology to vaccines. According to Mark Mitchnick, CEO, "Particle Sciences has been steadily building our drug delivery intellectual property portfolio, and this is one more significant step. Recently we presented SATx<sup>™</sup> at the American Chemical Society in a podium presentation that was very well received. Using this platform we are able to offer our clients a real alternative to typical ADC approaches, one that can be rapidly prototyped and does not require the use on any new chemical entities." Robert Becker, vice president biopharmaceutical sales and business development, added that "Particle Sciences has made a significant investment in both the formulation and analytic support of biologics. The SATx<sup>™</sup> technology is a disruptive nanoparticle platform that gives our clients new options for improving the potency, safety, and utility of both large and small molecule therapeutics that can't be found elsewhere. For clients looking to leverage their new biopharmaceuticals and vaccines, and those seeking to develop "bio-betters," the SATx<sup>™</sup> platform should be seriously considered and evaluated."

### March

### Althea's New Drug Formulation Technology Gains Attention from Two More Top Pharmaceutical Companies

PRNewswire: March 31, 2015 - SAN DIEGO, CA, U.S.A. -Ajinomoto Althea, Inc. ("Althea"), a leading provider of biopharmaceutical contract development and manufacturing services, announced today that it has added two more top pharmaceutical companies to its growing list of partners in developing and manufacturing cGMP-produced crystal-based drug products using Althea's Crystalomics® drug delivery technology. With these additional companies, a total of 4 out of 10 of the world's top pharmaceutical companies have already signed agreements with Althea since Ajinomoto's acquisition of Althea and the Crystalomics® technology. This proprietary Crystalomics<sup>®</sup> formulation technology is utilized to formulate and manufacture crystal suspensions of developed drug substance. Often, drug manufacturers encounter stability and delivery challenges for protein products including antibodies that require delivery at high concentration and low viscosity or must be administered frequently. Products formulated with the Crystalomics<sup>®</sup> technology can be delivered at low viscosity and high concentrations in a small volume. In addition, the Crystalomics® technology enables extended release of a week or more, transforming daily to weekly injections.

David Enloe, president and CEO of Althea, states, "We are very pleased to see a growing number of pharmaceutical companies implementing work with our Crystalomics<sup>®</sup> technology. We welcome the opportunity to support this growing list of partners by delivering regulatory compliant crystal suspension products that will overcome their high concentration delivery challenges. The Crystalomics<sup>®</sup> formulation technology has tremendous potential in drug development, promoting enhanced outcomes of drug treatments and improving compliance."

Althea's crystal suspension manufacturing services deliver a comprehensive set of service capabilities including Crystalomics<sup>®</sup> process development, in-process and release testing analytics, equipment qualification and validation, and complete cGMP bulk manufacturing fill and finish production.

### Neurotech Announces FDA Acceptance of Investigational New Drug Application and Clinical Trial Initiation of Novel Therapy for Wet AMD

PRNewswire: March 30, 2015 – CUMBERLAND, RI, U.S.A. – Neurotech Pharmaceuticals, Inc., announced today that the U.S. Food and Drug Administration (FDA) has accepted

## EGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLO

and communicated Neurotech's ability to proceed with its Investigational New Drug (IND) application to conduct a phase 2 clinical study of NT-503 Encapsulated Cell Therapy (ECT) for the treatment of recurrent subfoveal choroidal neovascularization secondary to age related macular degeneration (wet AMD).

The phase 2, randomized, active-controlled, masked study will commence immediately and enroll 150 patients. The safety and efficacy of one NT-503 ECT implant will be compared with aflibercept intravitreal injections every 8 weeks in patients who have been treated with at least three anti-VEGF injections and still have active disease. Patients will be followed for 2 years with a 12-month interim assessment.

"We are delighted to be a part of this important study," expressed study investigator David Boyer, M.D., senior partner at Retina-Vitreous Associates Medical Group and clinical professor of ophthalmology at the University of Southern California Keck School of Medicine. "The NT-503 ECT implant, essentially a reversible gene therapy, represents the future of intraocular drug delivery. To have a therapy that could effectively and continuously treat our AMD patients long-term without the burden of frequent injections is very exciting. It is also advantageous to have the option of removing the implant, if desired."

ECT is an intravitreal implant that houses a proprietary retinal pigment epithelial cell line genetically engineered to produce several therapeutically active biologics for at least 2 years. NT-503 is a novel vascular endothelial growth factor (VEGF) receptor protein that is continuously produced by the ECT platform.

"This is a significant milestone for our NT-503 ECT program," commented Quinton Oswald, chief executive officer of Neurotech. "Real-world injection frequencies often do not correlate with optimal treatment recommendations due to the enormous burden of monthly or bi-monthly injections and disease monitoring," he added. "We are one step closer to being able to give patients and physicians an efficacious, long-term therapy with a single outpatient surgical procedure."

### Columbia Laboratories Acquires Exclusive Worldwide License to a Novel Segmented Intravaginal Ring Delivery Technology

PRNewswire: March 30, 2015 – BOSTON, MA, U.S.A. – Columbia Laboratories, Inc. (Nasdaq: CBRX) ("Columbia" or "the company"), a specialty pharmaceutical company focused on the development of therapeutics for women's health, has licensed exclusive worldwide rights to a novel intravaginal ring ("IVR") technology for the delivery of one or more pharmaceuticals at different dosages and release rates in a single segmented ring.

This technology was developed by renowned scientists Dr. Robert Langer from the Massachusetts Institute of Technology ("MIT") and Dr. William Crowley from Massachusetts General Hospital ("MGH") and Harvard Medical School ("HMS"). Under separate agreements, Drs. Langer and Crowley have joined the company as strategic advisors to support the deployment of this technology and guide development of future product candidates.

"This technology affords the opportunity to expand intravaginal delivery of drugs to include larger molecules, such as peptides, alone and in combination," said Dr. Robert S. Langer, the MIT Department of Chemical Engineering David H. Koch Institute Professor and one of four living individuals who have received both the U.S. National Medal of Science and the U.S. National Medal of Technology and Innovation, the nation's highest scientific honors.

"A self-administered vaginal ring provides patients with a simplified drug delivery system and should improve compliance and therefore treatment effectiveness," said Dr. William F. Crowley, the Daniel K. Podolsky Professor of Medicine at HMS, chief of the Reproductive Endocrine Unit of the Department of Medicine at MGH, and director of the Harvard-wide Reproductive Endocrine Sciences Center, one of the eight Centers of Excellence in Translational Research of the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Currently available IVRs have simplified the delivery of medicine and are convenient and discreet; however, few diseases or conditions have been addressed due to technological limitations. Challenges include drug solubility, molecular characteristics, and desired controlled release profiles.

Due to its unique polymer composition and segmentation capability, the segmented IVR developed by Drs. Crowley and Langer has the ability to deliver drugs at different dosages and release rates within a single ring system. Drugs such as progesterone and leuprolide have already been tested using the technology and demonstrated sustained release for up to three weeks. The company has identified a number of product concepts that could address large market segments and will be prioritizing development of the first candidates in the coming months.

"This novel drug delivery technology aligns perfectly with our strategy to develop proprietary products targeting areas of unmet medical need in women, and we see numerous new product and life cycle management opportunities for it," said Frank Condella, Columbia's president and chief executive officer. "We look forward to combining the expertise of Drs. Langer and Crowley with the in-house formulation and drug development capability of our Molecular Profiles, Ltd., subsidiary to bring important new medicines to women."

Columbia has agreed to minimum annual expenditures to develop products using the vaginal ring technology and will make milestone-based payments to MGH/MIT when various stages of

### GLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOB

In the News continued from page 33

product development and commercialization are achieved. The company will also share a portion of any royalties or sublicense revenues received from products utilizing the segmented IVR technology with MGH and MIT.

Columbia is funding its proprietary product development program with operating cash flows driven by the global CRINONE® (progesterone gel) franchise and its pharmaceutical services business. The company intends to advance product candidates through to phase II proof-of-concept and will look to partner for later stage clinical trials and commercialization.

Recently, the company announced plans to initiate a phase II clinical trial for COL-1077 in women undergoing transvaginal pipelle-directed endometrial biopsy in the second quarter of 2015. COL-1077 is being developed as a sustained-release 10% lidocaine gel for vaginal administration, intended as an acute-use anesthetic for minimally invasive gynecologic procedures. Columbia is actively evaluating new product opportunities for advancement into development using this delivery platform as well. Additional programs will be announced as they clear internal development hurdles, including intellectual property filings, commercial assessments, and clinical development plans.

Columbia Laboratories, Inc. has a successful heritage in developing women's health focused pharmaceutical products including CRINONE<sup>®</sup> 8% (progesterone gel), which is marketed by Actavis, Inc., in the United States and by Merck Serono S.A. in over 60 additional countries worldwide. Columbia is leveraging its pharmaceutical development, clinical trial manufacturing, and advanced analytical and consulting services to advance an internal pipeline while generating revenue from pharmaceutical industry customers. For more information, please visit www.columbialabs.com.

### Genisphere's 3DNA<sup>®</sup> Drug Delivery Platform Achieves Success in Preclinical Treatment of Posterior Capsular Opacification (PCO)

PRNewswire: March 26, 2015 – HATFIELD, PA, U.S.A. – Genisphere LLC, provider of the 3DNA® nanotechnology platform, reported today it has achieved specific immunodepletion of problematic Myo/Nog cells implicated in posterior capsular opacification (PCO), a clouding of the eye lens that can be a complication of cataract surgery. The company envisions a wide application of this immunodepletion strategy in other fibrotic diseases and cancer and has recently completed in-licensing intellectual property and additional assets for targeting Myo/Nog cells for therapeutic purposes from LIMR Development Inc. (LDI), a for-profit subsidiary of the Lankenau Institute for Medical Research, where an early stage of the technology was developed.

Myo/Nog cells were discovered in the laboratory of Dr. Mindy George-Weinstein, and named for their ability to form muscle (Myo) and their production of Noggin, an inhibitor of bone morphogenetic proteins involved in cell communication. A unique monoclonal antibody (mAb) specifically recognizes these cells and has been used to identify, track, deplete, and isolate this population from embryonic and adult tissues. Genisphere has collaborated with Dr. George-Weinstein to study the ability of the mAb to target cells implicated in PCO, a disease that typically occurs in approximately 30% of adults and greater than 70% of children after cataract surgery. They reported specific immunodepletion of Myo/Nog cells, when the mAb was used as a targeting device on Genisphere's 3DNA® nanocarrier loaded with doxorubicin. The targeted 3DNA® approach is similar to that of an antibody drug conjugate (ADC) but delivers 100 times more of the drug to the targeted cells than an ADC and has no observed toxicity. Additional studies testing this formulation in rabbits undergoing cataract surgery are ongoing with Drs. Liliana Werner and Nick Mamalis, codirectors of the Intermountain Ocular Research Center at the University of Utah. Dr. Werner commented, "This is a preventative treatment of PCO, and the preliminary efficacy and safety results look very promising."

Dr. Mindy George-Weinstein, professor of biomedical sciences at the Cooper Medical School of Rowan University, stated, "Myo/Nog cells have also been found in a variety of tumors, where we predict they contribute to tumor growth. This targeted 3DNA immunodepletion strategy may be useful as an adjuvant therapy to reduce tumor expansion and recurrence."

Dr. Robert Getts, chief science officer of Genisphere, said, "Since the antibody has broad utility and 3DNA nanocarriers can deliver a variety of drug cargoes, we can easily generate targeted drugs for many of these indications." He added, "Genisphere's partnership model for development of nanotherapeutics has set the path forward for clinical testing and future commercialization of these and other candidates."

Genisphere LLC is a targeted drug delivery platform company. Genisphere's platform is a DNA-based nanotechnology called 3DNA<sup>®</sup>. 3DNA<sup>®</sup> 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<sup>®</sup> nanostructures are composed entirely of DNA, engineered and crosslinked 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<sup>®</sup> platform. For more information, please visit http://genisphere.com.

### Therapure Innovations Receives FDA Approval to Proceed with a Phase 1 Clinical Trial of the Targeted Liver Cancer Therapeutic TBI 302

Business Wire: March 25, 2015 – MISSISSAUGA, ONTARIO, Canada – Therapure Innovations, a division of Therapure Biopharma Inc., today announced that the U.S. Food and Drug Administration (FDA) has given the company approval to proceed with a phase 1 clinical trial of TBI 302, a targeted therapeutic for the treatment of liver cancer. TBI 302 is the first drug to emerge from Therapure's targeted drug delivery platform, which takes advantage of the natural clearance pathway of hemoglobin predominantly through the liver. TBI 302 consists of the chemotherapy drug floxuridine attached to hemoglobin, which serves as the drug carrier and targeting agent. The targeted drug delivery approach of TBI 302 is intended to deliver drugs to the liver while sparing other tissues from the toxicity of chemotherapy drug exposure.

"This technology addresses an area of unmet medical need that may provide a means to specifically deliver an active therapeutic to the site of the cancer and potentially provide a direct benefit to patients," said Dr. David Bell, vice president and chief scientific officer of Therapure. "Our company has extensive experience working with blood proteins and hemoglobin in particular, so we're excited to see this innovative product moving into the clinic."

"We're proud of this major milestone achieved by our Therapure Innovations division," said Nick Green, Therapure's president and chief executive officer. "Receiving the FDA's okay to initiate this trial speaks to the great team of skilled researchers, development specialists, and manufacturing experts who continue to advance our proprietary pipeline products. In a short period of time, this is our second product to advance into clinical trials in a second therapeutic area."

The phase 1 clinical trial is an open-label, multicenter study of TBI 302, which will evaluate the safety, tolerability and pharmacokinetics of TBI 302 following administration to patients with advanced liver cancer.

Liver cancer is the fifth most common cancer and the third leading cause of cancer-related deaths globally. When surgical removal of tumors is not an option, a range of chemotherapy drugs are used to manage the disease, but these can cause side effects in other tissues. Better methods are needed to target chemotherapy drugs to cancer cells while leaving healthy tissues unharmed.

# Moberg Pharma Announces Issue of U.S. Patent for Kerasal Nail

Business Wire: March 25, 2015 – STOCKHOLM, Sweden – Moberg Pharma AB (STO: MOB) today announced that the U.S. Patent and Trademark Office has issued U.S. patent no. 8,987,330 for Moberg Pharma's market-leading product Kerasal Nail<sup>®</sup>, an over-the-counter (OTC) product for fungal nails. The patent expires in 2034.

The new U.S. patent comprises composition of matter claims directed to novel formulations for topical application to the nails. Moberg Pharma is pursuing corresponding patent approval in all major territories.

Based on this innovation, Moberg Pharma launched the second generation of its market-leading product Kerasal Nail<sup>®</sup> in the United States last year in major drugstores including CVS, Walgreens, and Rite-Aid, mass retailers including Walmart and Target, and leading grocery chains including Publix and Safeway. Kerasal Nail is the leading product in the U.S. OTC fungal nail category with 22% market share in 2014 according to IRI, and it is available at more than 30,000 outlets. The product is also sold in more than 30 countries worldwide through distributors.

"The new Kerasal Nail patent provides long-term intellectual property protection for our flagship product in the United States. It also reconfirms our commitment to bringing innovation to underserved niches and our long-term goal to be the leading player in nail fungus," said Peter Wolpert, CEO of Moberg Pharma AB.

# Stemedica Obtains an Exclusive Worldwide License for Stem Cell Stabilization and Preservation Technologies

PRNewswire: March 24, 2015 – SAN DIEGO, CA, U.S.A. – Stemedica Cell Technologies Inc. (Stemedica) announced today that Universal Stabilization Technologies (UST) has granted to Stemedica subsidiary StemProtein, LLC, an exclusive worldwide license to its technology known as Preservation by Vaporization (PBV) for industrial-scale stabilization of stem cells and stem cell derivatives. This license will allow Stemedica and StemProtein to manufacture stem cell-secreted therapeutic proteins in a VitriLife<sup>™</sup> state that remain shelf stable and therapeutically active at ambient temperatures for two or more years.

"UST's technology immediately accelerates Stemedica's development of a wide range of products containing stem cell factors for consumer and medical markets worldwide," said Nikolai Tankovich, M.D., Ph.D., Stemedica's president and chief medical officer. "PBV significantly improves the bioactivity of preserved stem cell factors for reconstitution in many forms-from powders to gels, from bandages to liquids. PBV-preserved proteins are superior in activity compared with lyophilized proteins." Stemedica products currently in development include eye drops, inhalable dry powders, wound dressings, injectable (parenteral) solutions, nose drops, sublingual tablets, and a variety of skincare and dental products. "In addition to the significant consumer opportunities, we are optimistic about the role stabilized products may have in helping to treat a number of medical conditions including skin damage, eye diseases, and cardiovascular and neurological conditions and in working to prevent or to slow down disease development such as Alzheimer's disease," said Dr. Tankovich.

UST's Preservation by Vaporization is a unique technology that preserves the biological activity of stem cell proteins at room temperature and significantly cuts the time and cost of manufacturing compared with conventional methods of preservation while increasing final product yields as reconstituted in its various distribution and packaging forms. PBV technology provides an efficient process for converting stem cell factors into fine powders that retain their natural efficacy for eventual bulk processing and packaging of product for mass consumer and medical markets.

"I am pleased to enter into this collaboration with Stemedica," said Victor Bronshtein, Ph.D., founder of Universal Stabilization Technologies and inventor of PBV. "Stemedica's cGMP manufac-

### GLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOBE•AROUNDTHEGLOB

In the News continued from page 35

turing and its unmatched command of commercial scale-up technologies are cornerstones for manufacturing pharmaceutical and over-the-counter products for consumer and medical markets."

The patented PBV technology immobilizes biologicals in glassy carbohydrates (a VitriLife<sup>™</sup> state) that enable its stable storage and shipping without refrigeration. PBV preserves a mixture of macromolecules that are secreted by stem cells in culture. The thermostable mixture contains sensitive biologicals, such as cytokines, chemokines, growth factors, matricellular proteins, enzymes, mRNAs, and microRNAs.

"UST's propriety dosage format will enable Stemedica's preserved stem cell products to meet ambient temperature (-20 to +40°C) shelf-life standards for a pharmaceutical or over-the-counter product," said Yuri Kudinov, M.D., Ph.D., vice president of research at StemProtein. "Thermostable stem cell products will ensure the confidence of patients and prescribing physicians that a product provides the therapeutic activity listed on the label, not merely at the time of manufacture but at the time of use. This is not the case for many stem cell products now marketed through consumer channels."

Universal Stabilization Technologies, Inc. (UST) is a privately held service and product-development company based in San Diego, California. UST's mission is long-term stabilization (preservation) at high ambient temperatures of vaccines and other biopharmaceuticals, probiotics, blood, and other cells or cellular components. UST's patented industrial-scale Preservation by Vaporization (PBV) process technology makes it possible to achieve higher yields after drying and better stability during storage at ambient or even higher temperatures (including 37°C or higher) than is currently possible with conventional techniques such as freeze drying or spray drying. The PBV process has been successfully applied to make thermostable formulations of a wide range of biologics, including probiotic bacteria, live attenuated vaccines for human and animal markets, blood plasma, and other blood-derived products. The process is scalable for batch or continuous load operations and can be executed using a conventional freeze dryer.

Founded by Victor Bronshtein, Ph.D., UST has applied contemporary physics, physical biochemistry, and process engineering for development of advanced preservation technologies. The PBV platform extends into numerous business areas: pharmaceuticals, biopharmaceuticals, foods, cosmetics, and so on. For more information, visit www.vitrilife.com.

Stemedica Cell Technologies, Inc., is a specialty biopharmaceutical company that manufactures best-in-class allogeneic adult stem cells and stem cell factors. The company is a governmentlicensed manufacturer of cGMP, clinical-grade stem cells currently used in U.S.-based clinical trials for acute myocardial infarction, chronic heart failure, cutaneous photoaging, and ischemic stroke. Stemedica's products are also used on a worldwide basis by research institutions and hospitals for preclinical and clinical (human) trials. Stemedica is currently developing additional clinical trials for other medical indications using adult, allogeneic stem cells under the auspices of the FDA and other international regulatory institutions. The company is headquartered in San Diego, California, and can be found online at www.stemedica.com.

### Heron Therapeutics Reports Positive Results from Phase 1 Study of HTX-011

Business Wire: March 19, 2015 – REDWOOD CITY, CA, U.S.A. – Heron Therapeutics, Inc. (NASDAQ: HRTX), a biotechnology company, announced today positive results from a phase 1 clinical study of HTX-011, Heron's lead product candidate for the prevention of postoperative pain. HTX-011, which utilizes Heron's proprietary Biochronomer<sup>®</sup> drug delivery technology, is a long-acting formulation of the local anesthetic bupivacaine in combination with the anti-inflammatory meloxicam.

This placebo-controlled, phase 1 study evaluated single doses of 100, 200, and 400 mg of HTX-011 in healthy volunteers. The key results from the study are described below:

- The desired pharmacokinetic profile for both bupivacaine and meloxicam was achieved. Specifically, therapeutically relevant drug levels of bupivacaine were sustained for 2–3 days. This was achieved in the absence of the large initial peak of bupivacaine that is observed with commercially available formulations of the drug.
- Robust anesthetic activity that closely correlated with plasma bupivacaine concentrations was observed, with anesthetic effects persisting through 96 hours.
- All three doses were well-tolerated with no serious adverse events, clinically relevant ECG or laboratory changes, or premature discontinuations. Mild redness and bruising were seen at some injection sites due to the subcutaneous administration of the product in this healthy volunteer study.

"The effective management of pain without the use of opioids remains an important area of unmet medical need, and we are excited that HTX-011 could potentially provide a differentiated therapeutic profile with advantages compared with currently available pain management options," commented Barry D. Quart, Pharm.D., chief executive officer of Heron Therapeutics. "We are encouraged by these positive results supporting HTX-011's bestin-class potential and look forward to moving into phase 2 clinical development in the second quarter of this year."

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### **Calendar of Events**

### 2015

Pre-Conference Symposium on Drug Transport and Delivery Sponsored by CRS July 25 Edinburgh, Scotland www.nanotech.dtu.dk/crossflows/ crs-nordic-chapter

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

### Advances in Tissue Engineering Short Course Sponsored by CRS

August 12–15 Houston, TX, U.S.A. http://tissue.rice.edu/

13th International Nanomedicine and Drug Delivery Symposium (nanoDDS) September 16–18 Seattle, WA, U.S.A. www.nanodds.org 20th International Symposium on Microencapsulation October 1–3 Boston, MA, U.S.A. www.northeastern.edu/ims2015/contact

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