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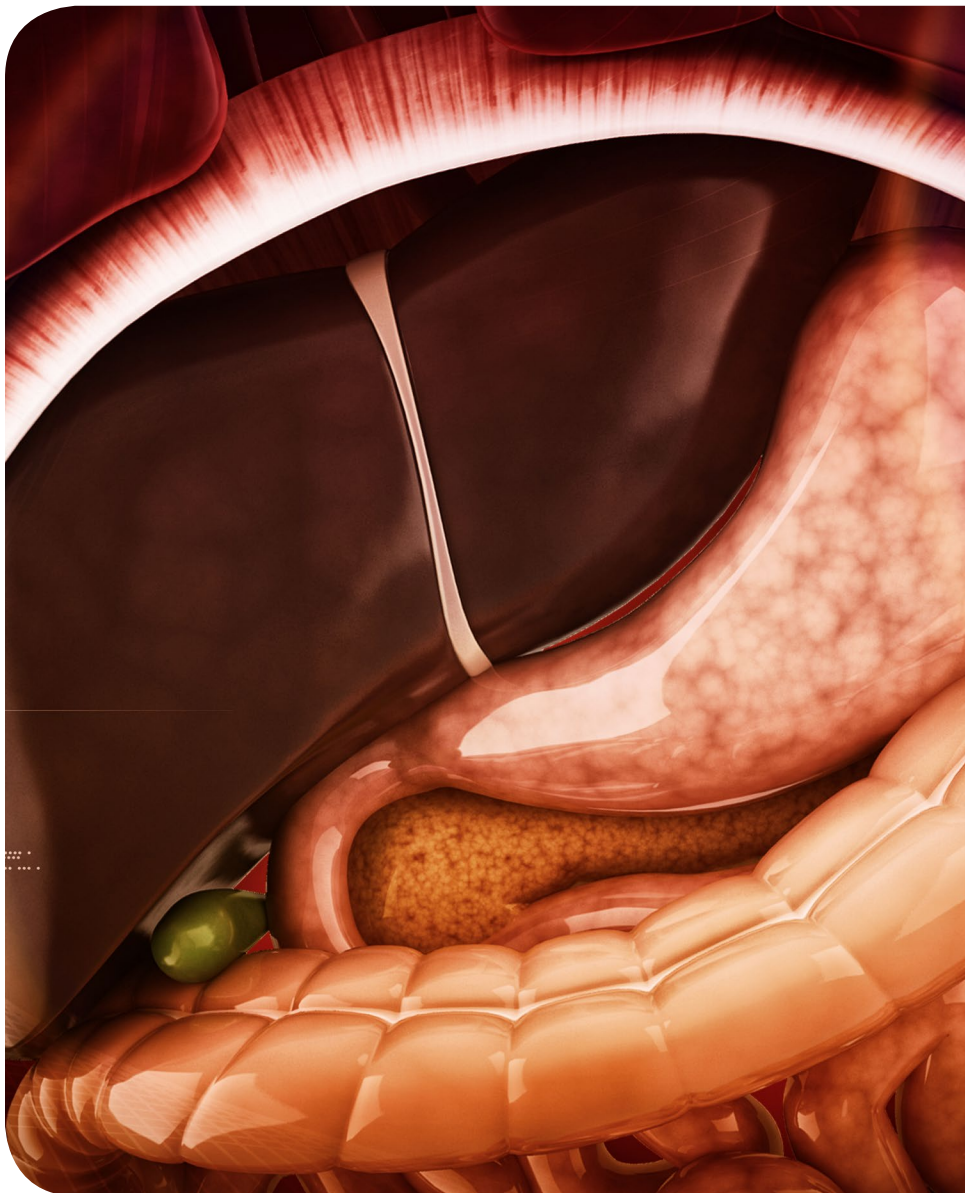
Dendritic Polyglycerol-Based  
Nanogels for Dermal Drug Delivery

Dynamic *In Vitro* Characterization of  
Micellar Structures in the GI Tract  
During Food Digestion Using SANS

Interview with Ali Khademhosseini  
at Harvard Medical School

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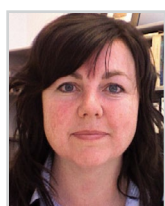




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**Rod Walker**  
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# CRS Newsletter

Leading  
Delivery Science  
and Technology

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Cover image: 3D illustration of a human anatomy digestive system cutaway © Liya Graphics / Shutterstock.com

## Editors

Charles Frey  
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## Yearning for the Sea

Antoine de Saint-Exupéry was a French writer, poet, aristocrat, journalist, and aviator. He lived from 1900 to 1944. He came to mind as I considered the energies and inspired work noted in this issue's interview with Prof. Ali Khademhosseini. Saint-Exupéry shared insightful and inspiring thoughts through memorable analogies from fundamental viewpoints. Here are a few of them:

*If you want to build a ship, don't drum up people to collect wood and don't assign them tasks and work, but rather teach them to long for the endless immensity of the sea.*

*The machine does not isolate us from the great problems of nature but plunges us more deeply into them.*

*It is in the compelling zest of high adventure and of victory, and in creative action, that man finds his supreme joys.*

*It is only with the heart that one can see rightly; what is essential is invisible to the eye.*

*Nobody grasped you by the shoulder while there was still time. Now the clay of which you were shaped has dried and hardened, and naught in you will ever awaken the sleeping musician, the poet, the astronomer that possibly inhabited you in the beginning.*

These translations are from various sources but likely carry critical elements of the messages Saint-Exupéry shared. Some contain a unique sense of optimism, and others have shades of darkness associated with failures to engage the self or others. New challenges are ever before us, and there is a sense of urgency associated with embracing opportunities and realizing one's potential. Be aware that a controlled release researcher and anyone associated with such work could fit rightly with the noble professions mentioned in the last quote.

There are ideas in these that we can relate to and draw from whether in the way we motivate and treat others or the way we motivate and treat ourselves. We are united in unique ways, and our constructive interactions arguably provide our greatest advantage. We are incredibly fortunate to work in professions that introduce fundamental benefits to society, and it is helpful to hold on to that notion.

In this newsletter, the contributors, the CRS Newsletter editorial team, and CRS staff have created another snapshot of current happenings in the field of controlled release and this society. I encourage you to read the Khademhosseini interview. Take a look at the science and the items in your interest area. Consider where you would like to contribute to the CRS "machine," and above all, build that yearning for the sea, whatever you conceive it to be, in yourself and others.

Chuck Frey ■



# Insight into the Progress of Biomedicine and Stem Cell Bioengineering at Harvard Medical School with Ali Khademhosseini

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



Ali Khademhosseini

Prof. Ali Khademhosseini is a professor of biomedical engineering and medicine at Harvard Medical School and a faculty member at the Harvard–Massachusetts Institute of Technology (MIT) Division of Health Science and Technology and at Brigham and Women's Hospital, as well as an associate faculty member at the Wyss Institute for Biologically Inspired Engineering. He also holds positions as a junior principal investigator at Japan's World Premier International–Advanced Institute for Materials Research (WPI-AIMR) at Tohoku University. He serves as an eminent scholar at Konkuk University in Korea and is a distinguished adjunct professor at King Abdulaziz University in Saudi Arabia.

He received both his BSc (1999) and MASc (2001) degrees in chemical engineering from the University of Toronto. He then joined Dr. Robert Langer's lab to secure his PhD in bioengineering from MIT (2005). Since then he has been an author on approximately 450 peer-reviewed journal articles and 60 book chapters, filed 20 patent or disclosure applications, and given over 250 invited seminars and keynote lectures. He has also been the editor of multiple books and journal special issues. He has been cited ~25,000 times and has an H-index of 82. He is an associate editor for *ACS Nano* and is on the editorial boards of numerous journals including *Small*, *RSC Advances*, *Advanced Healthcare Materials*, *Biomaterials Science*, *Journal of Tissue Engineering and Regenerative Medicine*, *Biomacromolecules*, *Reviews on Biomedical Engineering*, *Biomedical Materials*, *Journal of Biomaterials Science–Polymer Edition*, and *Biofabrication*. He is the chair of the Bionanotechnology Technical Activities Committee for the Institute of Electrical and Electronics Engineers (IEEE) Engineering in Medicine and Biology Society (EMBS).

His current research focus is on developing micro- and nanoscale biomaterials to control cellular behavior, with particular emphasis on developing engineered materials and systems for tissue engineering. He is also developing organ-on-a-chip systems that aim to mimic human response to various chemicals *in vitro*. His laboratory is developing technologies to control the formation of vascularized tissues with appropriate microarchitectures as well as regulating stem cell differentiation within microengineered systems.

His research work has been exemplary. For his research contributions, Prof. Khademhosseini has been recognized by over 40 major national and international awards. Among other recognitions, he received the CRS Young Investigator Award in 2013. During his early career, he was the proud recipient of the Presidential Early Career Award for Scientists and Engineers, the highest honor given by the U.S. government for early career investigators. He has received recognition from all three major engineering discipline societies: electrical (IEEE-EMBS award and IEEE Nanotechnology Award), chemical (Colburn Award from the American Institute of Chemical Engineers), and mechanical engineering (Y. C. Fung Award from the American Society of Mechanical Engineers). In 2007, *Technology Review* named him a TR35 recipient as one of the world's top young innovators.



Ali Khademhosseini in the lab.

**Q** Please describe the nature of biomaterials being used in your lab. What was the rationale behind development and application of these materials?

**A** Our lab uses a variety of different biomaterials. One of the major types that we use is a material called hydrogel. Hydrogels are particularly interesting as biomaterials because they are essentially hydrophilic networks of polymers, allowing us to mimic human tissues. We accomplish this by seeding the hydrogels with cells, and then the hydrogels mimic the natural cellular matrix of our tissues and can thus be used to make specialized materials for drug delivery.

*continued*

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*Giving a recent seminar on microengineered hydrogels for stem cell bioengineering.*

**Q** *Where have hydrogels been used in R&D? Have there been any potential commercial applications that have already come out or are in the pipeline as a result of your R&D?*

**A** The types of materials that we're making can be used for a variety of applications. For example, in tissue engineering, one can use these types of materials to make tissues. In surgery, one can use these hydrogels to make surgical glues and fillers. Also, these kinds of materials can be used for a variety of other cardiovascular applications. We are interested in translating these kinds of materials into real-world applications. We have several translational avenues that we are currently pursuing.

**Q** *What inspired you to stay in Boston as an academic after finishing your PhD?*

**A** I think that the Boston environment is particularly good for science because it has great academic institutions and hospitals, as well as a very entrepreneurial environment. Having done my PhD here, I was very lucky to have the opportunity to join the faculty at Harvard University and stay in the Boston area.

**Q** *Where do you see your research heading in next five years? What are some challenges that you would like to explore?*

**A** We are currently trying to fabricate tissues with improved functions and trying to further improve the technology to use these tissues for a variety of applications. For example, we believe that the tissues that we are making can be used to test drugs and drug delivery systems, which has several important consequences, such as the elimination of animal testing to determine drug efficacy. Some other applications include the use of these tissues in regenerative medicine, where we can eliminate the use of drugs completely by being able to recreate or regenerate the function of the tissue. Also, we're interested in making materials that will be useful in medical applications, from drug delivery systems to surgical biomaterials.

**Q** *Please mention some of the research that has come out of your lab that has made the most impact on scientific research.*

**A** We've published a variety of different papers that we are excited about; for example, we've popularized the use of particular types of hydrogels that have now been widely used by many different investigators. We've also made gels composed of elastin and gelatin that are light sensitive and can cross-link upon light exposure. In our other types of work, we've enabled the fabrication of tissues using modular approaches. The idea here is that we are able to create building blocks of tissues and then assemble them together to generate larger tissue structures using a variety of different processes, such as programmable glues.

We're also interested in 3D printing, so we have developed approaches where we can use 3D approaches to make tissues that are vascularized, along with other types of innovations.

**Q** *Please mention some of the research topics (not from your lab) that have caught your interest and can have a significant impact in science.*

**A** There are a number of different emerging research areas that will have significant impact. Many of these innovations are at the interface of different disciplines. For example, there is the new gene editing technique based on CRISPR CAS 9, which appears to be exciting for a variety of different biomedical applications; this is something that has really revolutionized the field. There are other advances in cell manipulation techniques, things related to optogenetics, which is an interesting technique that uses light to modify cellular tissues. Additionally, the ability to engineer the genomes of different organisms using synthetic biology is also interesting. All of these research areas merge well with the ability to make materials such as tissues, and so I think these are enabling technologies for our research.

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

**A** My job keeps me busy, but I try to spend time with friends and family as much as possible doing a variety of things. For example, I like to travel, and I'm particularly interested in different forms of art.

**Q** *We would appreciate any career advice you can give.*

**A** You have to find what your passion is and become really inspired by what your interests are. Once you figure out what your passion is, then you have to just pursue it and don't deviate from the path of your passion. Any successful person has to go through many failures and deal with constant challenges, so it's important to learn to problem solve and overcome challenges. ■



*Enjoying paint night in Boston.*

# Dynamic *In Vitro* Characterization of Micellar Structures in the GI Tract During Food Digestion Using SANS

Oljora Rezhdo,<sup>a,b</sup> Selenia Di Maio,<sup>c</sup> Peisi Le,<sup>d</sup> Kenneth Littrell,<sup>c</sup> Sow-Hsin Chen,<sup>d</sup> and Rebecca Carrier<sup>a</sup>

## Introduction

Food can significantly impact the bioavailability of oral drugs through multiple mechanisms including enhancement of solubility and dissolution kinetics, enhancement of permeation through the intestinal mucosa, and so on. The effect of food on drug absorption, however, is currently not amenable to quantitative predictions in part due to the multiple complex dynamic processes that can be impacted by food. Quantitative mechanistic analysis of processes significant to food function could enable effective oral delivery of drugs and nutritive supplements. Ingestion of food triggers a cascade of processes that change the physical and chemical nature of the gastrointestinal (GI) milieu and directly affect the behavior of oral compounds in the GI tract. For example, the digestion of lipids, a major ingredient in food, can impact both lipid emulsions and other colloidal species (most notably micelles) into which digestion products partition. Size and structure of colloids are important to study, because they directly affect oral compound partitioning and capacity to serve as a vehicle for compound transport along the GI tract. In this study, we have characterized the colloidal structures in the intestinal milieu during an *in vitro* simulated model food digestion. Milk was chosen as a model food due to its structural simplicity and its common use in the Western diet. Changes in size and shape of the colloidal structures were monitored as a function of digestion time using small-angle neutron scattering (SANS). The results obtained provide a physical conceptual framework and parameters such as volume, surface area, and shape of colloids as well as their evolution over time, which are essential tools needed in developing mechanistic expressions that describe processes affecting drug and nutrient absorption. Incorporating these expressions into a systems-based model that explicitly considers the impact of food-drug interactions on the simultaneous dynamic processes impacting overall absorption (Figure 1) may enable improved quantitative pharmacokinetic predictions and facilitate rational design of effective drug delivery strategies.

## Experimental Design

An outline of the SANS technique is shown in Figure 2. We prepared a model milk solution in the laboratory containing caseins (33 g/L), lactose (53 g/L), triolein (32 g/L), and CaHPO<sub>4</sub> (46 mM) in buffer at pH 6.5. The *in vitro* gastric

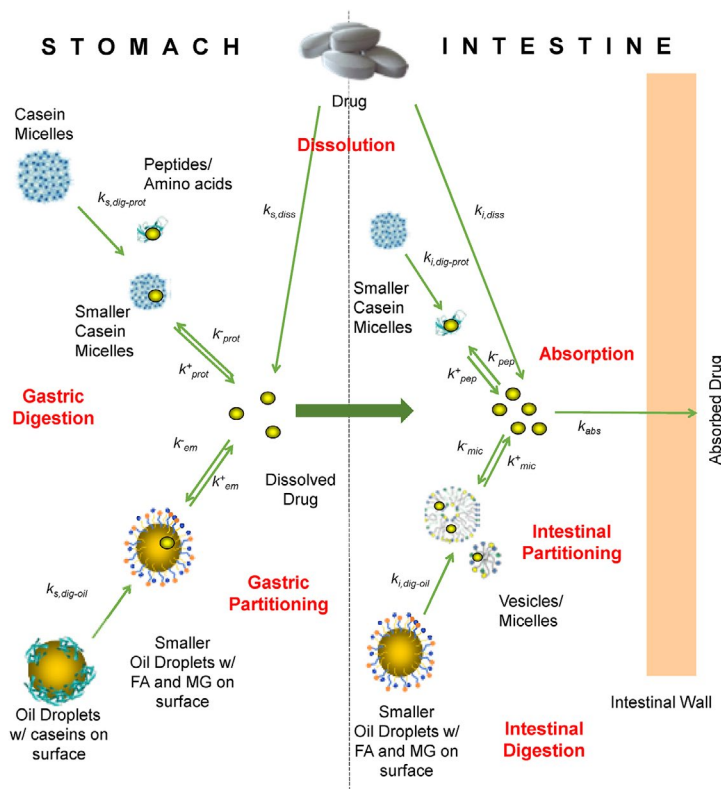


Figure 1. Mechanistic and kinetic analysis of the model system.

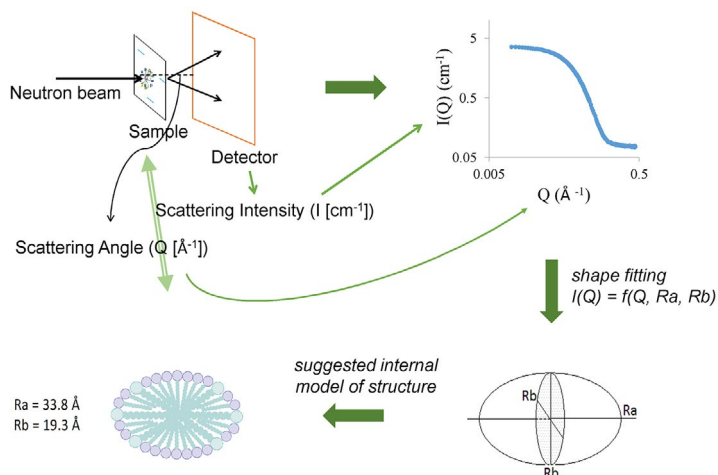


Figure 2. Overview of the SANS technique.

continued

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digestion process utilized rabbit gastric extract, with 1M HCl as needed for pH adjustment. The *in vitro* intestinal digestion used porcine pancreatic extract, 100 mM Trizma maleate, 65 mM NaCl, 10 mM CaCl<sub>2</sub>, 12 mM sodium taurodeoxycholate, 4 mM lecithin, chyme from the *in vitro* gastric digestion, and 0.2M NaOH as needed for pH adjustment.<sup>1</sup> Samples were collected throughout digestion using appropriate enzymatic inhibitors to monitor and quantify the structural evolution of colloidal structures during digestion.

Separate mixtures of bile components with products of digestion were also prepared and analyzed using SANS to determine the impact of each digestion component (e.g., digested caseins, diglycerides, monoglycerides, and fatty acids) on the structure of bile micelles.

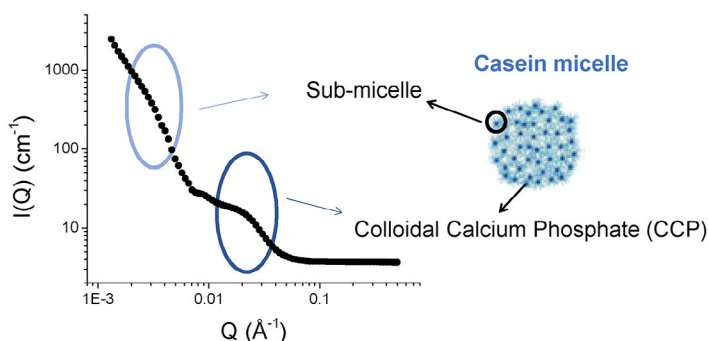
## Results and Discussion

**Micellar Structures in the Stomach.** Two types of colloidal structures were present in simulated milk: oil droplets and casein micelles. The size of oil droplets was analyzed with dynamic light scattering and a Coulter counter. The structure of casein micelles was analyzed with SANS. The nanocluster structure similar to that reported in the literature was observed by comparing the shape of the scattering intensity plots (Figure 3).<sup>2</sup>

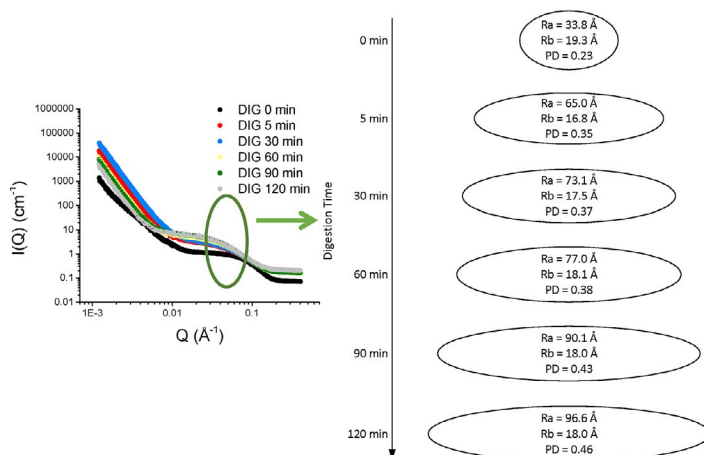
In the presence of gastric enzymes, casein digestion generates peptides and amino acids that associate with the aqueous phase, making the casein micelles smaller in size. In contrast, lipid digestion generates fatty acids and diglycerides only, which remain on the surface of the oil droplets, where lipolysis occurs.

**Micellar Structures in the Intestine.** As casein micelles are completely disintegrated in the stomach, partially due to proteolysis and partially due to protein precipitation by the low gastric pH, casein micelles are no longer present in the intestine. Only two types of colloidal structures were present during intestinal digestion: the oil droplets and the bile micelles. Oil droplets were again analyzed using dynamic light scattering, whereas bile micelles were analyzed using SANS. SANS showed the bile micelles were in the shape of cylinders or prolate spheroids that elongated along the longer axis during digestion (Figure 4). Lipid digestion continued to generate fatty acids and diglycerides as well as monoglycerides at this step. Diglycerides remained on the surface of the oil droplets, whereas fatty acids and monoglycerides partitioned between the oil and bile micelles. The swelling of bile micelles during digestion was caused by the insertion of fatty acids and monoglyceride molecules into the structure of the micelles.

**Modeling the Volume of Bile Micelles.** Mechanistic models aiming to predict drug behavior in the GI tract, and ultimately absorption in the presence of food, require a thorough characterization of colloidal structures in terms of colloid area and volume. In addition, as proteolysis and lipolysis affect colloid area and volume, the impact of the amount of micelle-bound fatty acids and monoglycerides on the volume of bile micelles, for example, needs to be quantitatively determined. We obtained empirical functional relationships between volume of micelles and concentration of fatty acids and monoglycerides (Figures 5 and 6). The results allowed us to obtain partition coefficients for oleic acid and for monoolein in a mixture of oil droplets and bile micelles. Ongoing work in our lab is focusing on using molecular modeling tools to achieve a better conceptual understanding of monoglyceride and fatty acid affinity for bile micelles on a molecular level.



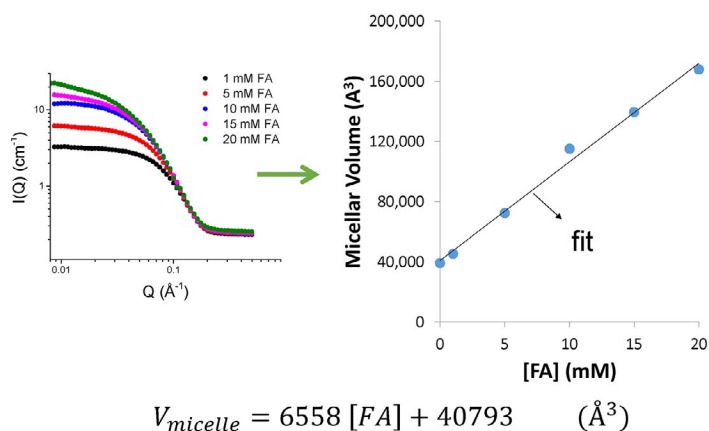
**Figure 3.** SANS plot of casein micellar structures in simulated gastric fluids: scattering angle,  $Q$ , versus scattering intensity,  $I(Q)$ . Right: structure of casein micelles consisting of casein clusters (sub-micelles) held together by colloidal calcium phosphate.



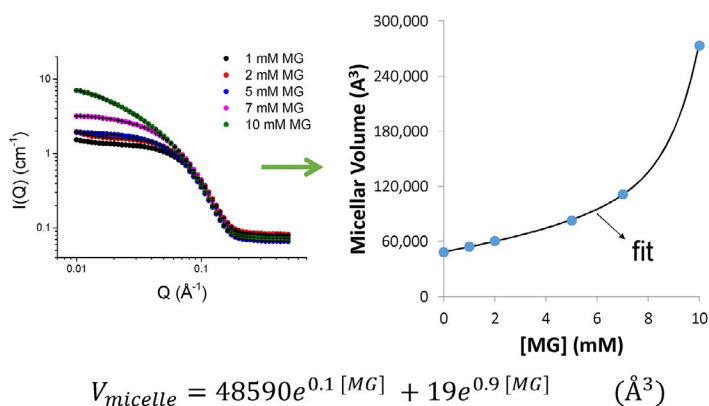
**Figure 4.** SANS plot of micellar structures in the intestine: scattering angle,  $Q$ , versus scattering intensity,  $I(Q)$ . Right: shape fitting, as described in Figure 2.

continued





**Figure 5.** Fitting of the relationship between the concentration of micelle-bound fatty acids (FA) and micelle volume.



**Figure 6.** Fitting of the relationship between the concentration of micelle-bound monoglycerides (MG) and micelle volume.

Combined effects of fatty acids and monoglycerides on the volume of micelles are currently being explored. The quantitative analysis of micellar volume will be:

- Combined with lipid digestion kinetic models to predict changes in volume of the micelles during digestion.
- Used to determine the concentration gradient serving as the driving force for drug partitioning from the aqueous environment into the bile micelles.
- Used to predict micellar volume changes during the absorption of fatty acids and monoglycerides.
- Incorporated into an overall model describing the drug absorption rate and ultimately a pharmacokinetic profile.

### Conclusion

We successfully monitored and analyzed the structural changes of the bile micelles during the digestion of a model food in real time. We are developing relationships that model and predict the volume changes of the bile micelles as a function of lipolysis. We are also developing kinetic expressions that relate the volume of micelles to drug and nutrient partitioning across the phases present in the GI tract during digestion. Coupled with kinetic drug dissolution and absorption expressions, we will ultimately predict drug pharmacokinetic profiles.

### Acknowledgements

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# Dendritic Polyglycerol-Based Nanogels for Dermal Drug Delivery

Maria Molina,<sup>a</sup> Madeleine Witting,<sup>b</sup> Marcelo Calderón,<sup>a,c</sup> and Sarah Hedtrich<sup>c,d</sup>

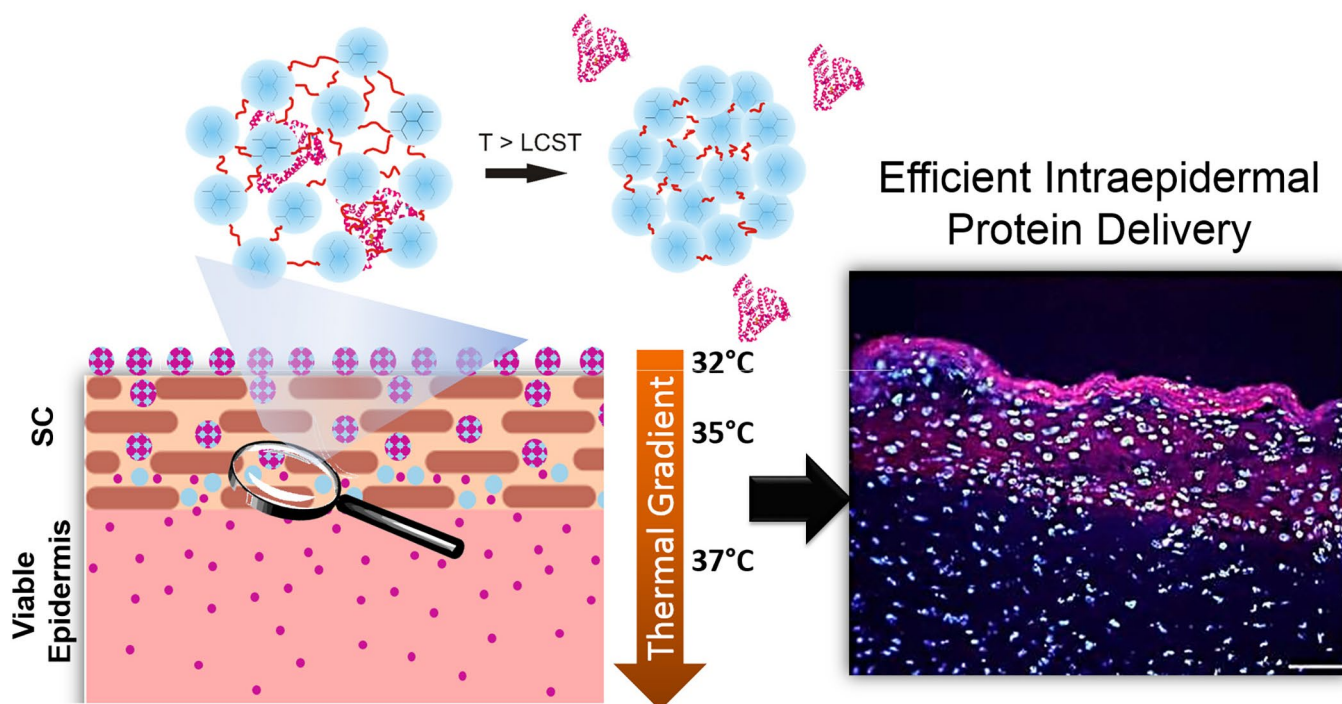
## Introduction

Therapeutically relevant proteins such as antibodies, growth factors, and enzymes play an increasing role in the treatment of malignant and autoimmune diseases. However, they often suffer from insufficient stability and poor bioavailability. A suitable method to increase protein stability might be the noncovalent encapsulation into polyglycerol-based nanogels. For drug release, environmental stimuli such as pH or temperature can be used to initiate a controlled and targeted release.<sup>1,2</sup> By crosslinking poly(*N*-isopropylacrylamide), a thermosensitive polymer, with dendritic polyglycerol, thermoresponsive nanogels were developed.<sup>3</sup> The nanogels were characterized regarding their protein loading and release, maintenance of protein structure and bioactivity, and stimuli-responsive cutaneous delivery resulting in efficient intraepidermal protein transport and restoration of the skin barrier function, particularly in diseased skin (Figure 1).

## Experimental Methods

The thermoresponsive nanogels were synthesized following the procedure described by Cuggino et al. by precipitation polymerization.<sup>3</sup> After purification of the nanogels the proteins were encapsulated by diffusion. The particle sizes and dispersity were measured by dynamic light scattering. Protein release was analyzed with high-performance size-exclusion chromatography using UV and fluorescence detection.

Protein stability over time was investigated at 25°C for up to 4 weeks. Furthermore, the activity of L-asparaginase was measured after four freeze-thaw cycles or in skin models. The amount of protein in the stratum corneum and viable epidermis were semiquantitatively



**Figure 1.** Protein release triggered by the thermal gradient within the skin. © 2015, reprinted with permission from Elsevier.<sup>2</sup>

*continued*

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determined using immunohistology. Moreover, the effects of the therapeutic protein transglutaminase 1 were evaluated in transglutaminase-deficient skin models. Skin penetration experiments were performed using pig skin mounted onto static-type Franz cells and according to validated test procedures. For data analysis, cross sections (5  $\mu\text{m}$ ) were subjected to normal and fluorescence light microscopy. To simulate barrier-disrupted skin, 30 times tape-stripping of the skin surface was performed.

To evaluate the barrier function, skin absorption tests with radiolabeled testosterone were performed according to validated procedures.<sup>4</sup>

## Results and Discussion

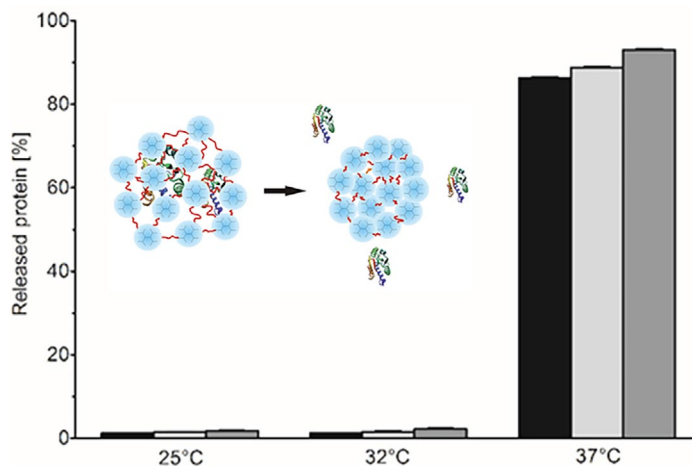
The particle size of the nanogels increased from 100 to 207 nm after the protein encapsulation and decreased to  $170 \pm 3$  nm above the transition temperature ( $34\text{--}35^\circ\text{C}$ ).

Release experiments of bovine serum albumin showed successful protein release up to 100% above the transition temperature. As intended, the nanogel stayed stable at temperatures below the trigger point of  $34^\circ\text{C}$  (Figure 2). The protein stability was studied through four freeze-thaw cycles. As can be seen in Figure 3A, a solution of L-asparaginase showed a loss of bioactivity of  $\sim 8\%$  after four freeze-thaw cycles, whereas for L-asparaginase-loaded nanogels only a decrease of  $\sim 4\%$  was observed. Furthermore, after storing free and nanogel-loaded L-asparaginase for 2 and 4 weeks at  $25^\circ\text{C}$ , a reduced bioactivity (Figure 3B), reduced tetramer amounts, and increased aggregation of unloaded L-asparaginase were observed.

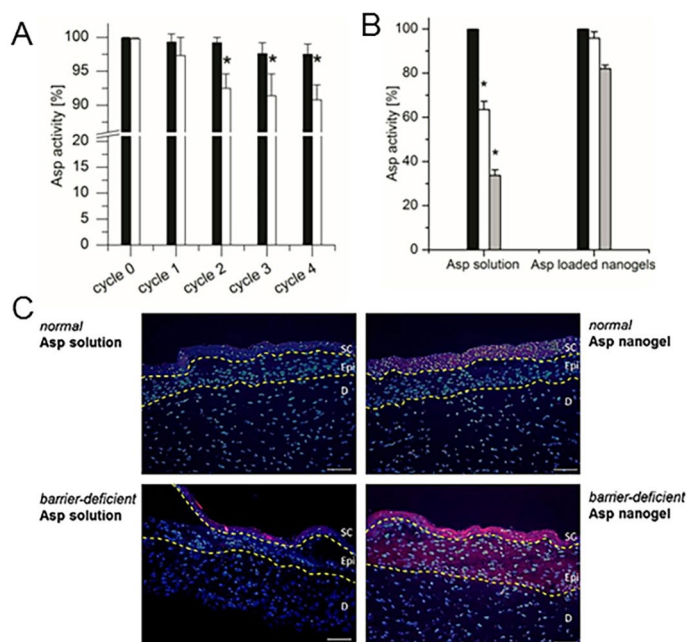
In the next step, we studied the absorption of free L-asparaginase and L-asparaginase-loaded nanogels in normal and barrier-deficient skin models (Figure 3C). The application of free protein did not result in intraepidermal penetration in normal or barrier-deficient skin models. In contrast, significant amounts of L-asparaginase were detected in the viable epidermis of barrier-deficient skin models following the application of the loaded nanogels, as shown by a marked red staining of the viable epidermis and the stratum corneum; no penetration was seen in normal skin models.

In the same manner and as a proof of concept of topical protein substitution, the nanogels loaded with the therapeutic protein transglutaminase 1 were applied onto transglutaminase-deficient skin models. Efficient protein delivery into the viable epidermis of transglutaminase-deficient skin models (Figure 4A) was observed.

Moreover, the barrier function was evaluated by skin permeation testing of testosterone (Figure 4B). Whereas in normal skin models  $\sim 1.5$   $\mu\text{g}/\text{cm}^2$  of testosterone permeated through the skin within 6 h, in transglutaminase-deficient skin models  $\sim 7.5$   $\mu\text{g}/\text{cm}^2$  was measured. After application of transglutaminase-loaded nanogels, the skin barrier function was restored, as indicated by a reduced testosterone permeation of  $\sim 2$   $\mu\text{g}/\text{cm}^2$ . This value, comparable to the barrier function of normal skin models, proves the restoration of the barrier function in transglutaminase-deficient skin models.



**Figure 2.** Release of bovine serum albumin from loaded nanogels after 1 h (black bars), 2 h (light grey bars), and 4 h (dark grey bars).



**Figure 3.** (A) Activity of loaded (black bars) and free L-asparaginase (Asp) (white bars) following four freeze-thaw cycles. (B) Activity of loaded and free L-asparaginase of freshly prepared samples (black bars), after 2 weeks (white bars), and after 4 weeks (gray bars) of storage at  $25^\circ\text{C}$ . (C) Skin penetration of L-asparaginase in normal and barrier-deficient skin models following the application of loaded poly(*N*-isopropylacrylamide)-dendritic polyglycerol nanogels and the control solution. © 2015, reprinted with permission from Elsevier.<sup>2</sup>

## Conclusion

Our data showed that thermosensitive nanogels are suitable and promising carrier systems for labile drugs such as biomacromolecules. Despite harsh chemical conditions, efficient encapsulation in the nanogels and subsequent delivery of the proteins in therapeutically relevant concentrations into the viable epidermis of barrier-deficient skin without loss of protein activity was achieved.

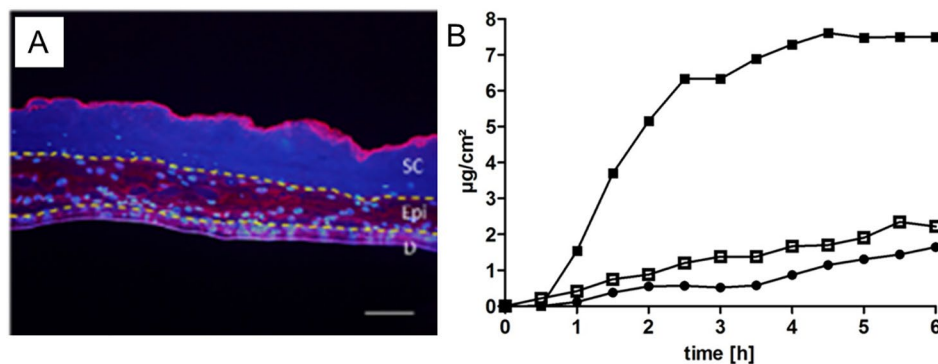
Moreover, the nanogels were able to stabilize and maintain the biological function of labile proteins. Finally, we provided the proof of concept that the delivery of the exemplary therapeutic protein transglutaminase 1 into transglutaminase-deficient skin was able to restore the skin homeostasis and to improve the skin barrier function.

## Acknowledgements

Financial support was provided by the Bundesministerium für Bildung und Forschung (BMBF) through the NanoMatFutur award (13N12561) to Prof. Calderón and a grant from the German Research Foundation to Dr. Küchler (DFG; KU 2904/2-1). Furthermore, we greatly acknowledge the support of the SFB 1112, projects A04 and C02. Dr. Molina acknowledges the Alexander von Humboldt Foundation for a postdoctoral fellowship.

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**Figure 4.** (A) Protein delivery into transglutaminase-deficient skin models after the application of transglutaminase-loaded nanogels. (B) Permeation of 1,2,6,7-<sup>3</sup>H-testosterone through normal (●), transglutaminase-deficient (■), and treated transglutaminase-deficient skin models (□). © 2015, reprinted with permission from Elsevier.<sup>2</sup>





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SUPPLY

## Congratulations to the 2016 Award Winners

CRS is honored to continue the tradition of recognizing the excellence of our members. Please congratulate the awardees on their well-earned commendation. Find biographies of awardees on the CRS website.

### Distinguished Service Award

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*The Distinguished Service Award is presented to a CRS member who has exhibited exceptional commitment and service to the society and is selected by the Board of Directors.*



**Ian Tucker**  
*University of Otago, New Zealand*

### Founders Award

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*The society grants this honor to a current CRS member who is internationally recognized for outstanding contributions in the science and technology of controlled release.*



**Hans E. Junginger**  
*Leiden University, Germany*

### College of Fellows

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*The College of Fellows recognizes those members who have made outstanding contributions to the field of delivery science and technology over a minimum of 10 years. Contributions may have been technical, scientific, and/or managerial in one or more fields of research, commercial development, education, and/or leadership within the areas of interest to CRS. Fellowship is the most prestigious level of membership in CRS.*



**Elias Fattal**  
*University of Paris Sud, France*

### CRS T. Nagai Postdoctoral Research Achievement Award

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*Cosponsored by The Nagai Foundation Tokyo*

*This award recognizes an individual postdoc who has recently completed postdoctoral research in controlled release science and technology and the postdoc's advisor, who played an integral role in the achievements.*



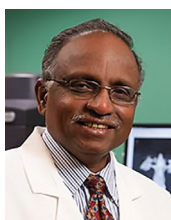
**Koen Raemdonck**  
*Ghent University, Belgium*



**Marilyn Martinez**  
*FDA Center for Veterinary Medicine, U.S.A.*



**Stefaan C. De Smedt**  
*Ghent University, Belgium*



**Vinod Labhasetwar**  
*Cleveland Clinic, U.S.A.*

### Young Investigator Award

---

*This award recognizes a CRS member who has made outstanding contributions in the science of controlled release and is 40 years of age or younger in the year the award is presented.*



**Ryan Donnelly**  
*Queen's University Belfast, United Kingdom*



**Steven Schwendeman**  
*University of Michigan, U.S.A.*

*continued*

## Jorge Heller Journal of Controlled Release Outstanding Paper Award

Cosponsored by Elsevier

*This award recognizes an outstanding regular paper related to the science of controlled release (not an invited, review, or special meeting paper) that was published during 2015 in the Journal of Controlled Release.*



**Robert Carlisle**  
*University of Oxford, United Kingdom*

*Increasing the density of nanomedicines improves their ultrasound-mediated delivery to tumours. J. Controlled Release 210: 10-18 (2015).*

## Drug Delivery and Translational Research Outstanding Paper Award

Cosponsored by Springer

*This award recognizes outstanding research in the field of drug delivery and translational research that was published during 2015 in Drug Delivery and Translational Research.*



**Andrés J. García**  
*Georgia Institute of Technology, U.S.A.*

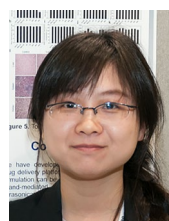
*Engineered VEGF-releasing PEG-MAL hydrogel for pancreatic islet vascularization. Drug. Deliv. Transl. Res. 5: 125-136 (2015)*

## CRS-Merck Graduate Research Advances in Delivery Science Award

*This award was presented to six students who presented exceptional science in drug delivery at the Poster Pub that took place during the 2016 CRS Annual Meeting in Seattle. Each recipient received a \$1,500 honorarium and an award certificate.*



**Maja Thim Larsen**  
*Aarhus University, Denmark*  
“Endosomal FcRn-dependent trafficking of albumin.”



**Yue Lu**  
*University of North Carolina, U.S.A.*  
“Transformable liquid-metal nanomedicine.”



**Alice Melocchi**  
*Università Degli Studi Di Milano, Italy*  
“Development of injection-molded capsular devices for pulsatile and colonic delivery through the application of fused deposition modeling (FDM) 3D printing.”



**Surojit Sur**  
*Johns Hopkins Kimmel Cancer Center, U.S.A.*  
“PRINT: A protein bioconjugation method with exquisite N-terminal specificity.”



**Johan Unga**  
*Teikyo University, Japan*  
“Development of a freeze-dried lipid-stabilized nanobubble for ultrasound imaging and gene delivery.”



**Christine Wang**  
*University of Washington, U.S.A.*  
“Junction opener protein increases nanoparticle accumulation in solid tumors in a size-dependent manner.”

## Allan Hoffman Student Travel Grant

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*Congratulations to the following students who received the CRS Foundation Allan Hoffman Student Travel Grant to attend the 2016 CRS Annual Meeting in Seattle, Washington.*

**Nicole Bisset**, Monash University, Australia

**Anna Blakney**, University of Washington, U.S.A.

**Alice Gaudin**, Yale University, U.S.A.

**Roun Heo**, Sungkyunkwan University, Korea

**Samuel Jativa**, University of Miami, U.S.A.

**Matthias Kuhlmann**, Aarhus University, Denmark

**Pierre Maudens**, University of Geneva, Switzerland

**Kevin McHugh**, Massachusetts Institute of Technology, U.S.A.

**Min Sung Suh**, University of Connecticut, U.S.A.

**Dedeepya Uppalapati**, University of Auckland, New Zealand



Student Travel Grants are named in honor of Controlled Release Society leaders who have made exceptional lifetime contributions to delivery science. The CRS Foundation Board has selected **Robert Langer** to be honored at the 2017 CRS Annual Meeting, July 16–19 in Boston, Massachusetts, for his achievements and his leadership. At this time, the CRS

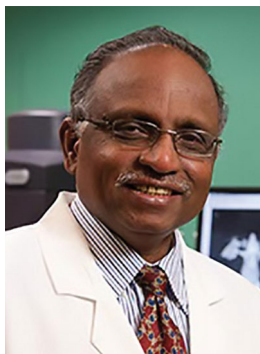
Foundation is requesting donations to fund these travel awards and allow the next generation of CRS leaders to meet and learn from Dr. Langer.

Donate now on the CRS website: [www.controlledreleasesociety.org/about/foundation/Pages/Donate.aspx](http://www.controlledreleasesociety.org/about/foundation/Pages/Donate.aspx). ■



# Drug Delivery and Translational Research Update

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



*Vinod Labhasetwar*

## **DDTR First Impact Factor 1.887**

We are pleased to announce the first *DDTR* impact factor (IF) of 1.887. This two-year IF is based on total number of citations in 2015 for the articles published in 2014 and 2013. The five-year IF is 1.917, which is the average number of times articles from the journal published in the past five years have been cited. Considering that *DDTR* began publishing in 2011 and the journal has been indexed recently (2015) in PubMed, a widely searched and used database, the first IF that the journal received is an important milestone. Since indexing in PubMed, we have noticed an increased number of citations. Compared with that in July 2015, the number of citations this year during the same time period has increased by 150%, and hence we anticipate that the 2016 IF of the journal will be higher. The average number of downloads per article from *DDTR* is around 250. The journal has also seen a greater than 70% increase in submissions compared with the previous year. With a merger between Nature Publishing Group, Palgrave Macmillan, Macmillan Education, and Springer Science+Business Media, *DDTR* is now a part of the newly formed Springer Nature. With that merger, *DDTR* is expected to reach an ever-growing multidisciplinary audience.

Consider submitting your high-quality basic and clinical research and review articles for greater visibility and expanding your reach to the global community. Submit your best research or clinical article to compete for the 2016 *DDTR* Outstanding Research Paper Award. Visit the CRS website for further details. CRS members have free access to articles published in *DDTR* as a membership benefit. Visit the CRS website for instructions on how to download articles.

## **Special Issue Under Development: Late Stage Development of Drug Delivery Systems**

This special issue will showcase emerging drug delivery approaches that have achieved significant milestones in clinical applications. Topics include various drug delivery systems and devices currently in clinical trials for both small and large molecules including proteins and genes, with a focus on their development strategies, drug product design, manufacturing insights, stability study design, lyophilization approaches, and targeted delivery approaches in both polymeric and lipid systems. Contact the guest editors if you wish to submit an article to this special issue: Keyur Gada ([keyur.s.gada@gmail.com](mailto:keyur.s.gada@gmail.com)) and Vishwesh Patil ([patil.vishwesh@gmail.com](mailto:patil.vishwesh@gmail.com)), Biogen, Cambridge, MA, U.S.A.

## **Special Issue: Advances in Technology and Business Potential of New Drug Delivery Systems (Volume 6, Issue 4, 2016)**

This *DDTR* special issue materialized from the 14th international symposium of the CRS India Local Chapter on Advances in Technology and Business Potential of New Drug Delivery Systems, organized at the Institute of Chemical Technology, Mumbai, India. The issue encompasses an eclectic blend of review and research papers pertaining to different aspects of novel drug delivery. The issue gives insight into the upcoming strategies in novel drug delivery science that hold strong business opportunities to drive the pharmaceutical business.

## **About the Guest Editors**



**Vandana B. Patravale** is a professor of pharmaceuticals at the Department of Pharmaceutical Sciences and Technology of the Institute of Chemical Technology, Mumbai, India. She has over 100 refereed publications, 9 book chapters, 4 granted patents, 24 patents in the pipeline, and 3 trademark registries to her credit and has handled many national and international projects. She has worked in close collaboration with industry and holds an extensive experience of approximately 25 years in the field of pharmaceutical sciences and technology. Her areas of expertise include conventional and modified release dosage forms, formulation strategies to enhance bioavailability and/or targeting, medical device development (coronary stents, intrauterine devices), nanodiagnostics, and novel nanocarriers with major emphasis on malaria, cancer, and neurodegenerative disorders. She has published two books, *Nanotechnology in Drug Delivery—A Perspective on Transition from Laboratory to Market* from Woodhead Publishing (now Elsevier) and *Pharmaceutical Product Development: Insights into Pharmaceutical Processes, Management and Regulatory Affairs* from CRC Press (Taylor and Francis).





**John I. Disouza** is a professor in pharmaceutics and principal at Tatyasaheb Kore College of Pharmacy, Kolhapur, India. He has over 15 years of teaching and research experience. He also has an executive MBA (higher education) degree. He has written two books, *Experimental Microbiology* and *Biotechnology and Fermentation Processes*, and has published over 50 research papers in peer-reviewed journals. He has worked in diverse research areas including herbal formulations; micro/nanoparticulates; self-emulsifying, liposomal, fast, and modified release drug delivery systems; and so on. His research areas of interest are probiotics, novel diagnostic tools and therapies in cancer, and structural modifications of natural polymers for their pharmaceutical potential. He is an active consultant to the pharmaceutical industry.



**Munira Momin** is a professor and head of the Department of Pharmaceutics and currently serving as a principal (I/c) at SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, India. She obtained her MPharm (pharmaceutics) from L.M. college of Pharmacy, Gujarat University, Ahmedabad, India. She received a gold medal (pharmaceutics) in her BPharm. Her PhD (pharmaceutical sciences) is on targeted drug delivery for phytoconstituents. She is a recipient of the Prof. M. L. Khurana Memorial Award for Best Research Paper published during the year 2008 in *Pharmaceutics and Bio-Pharmaceutics*. Her research interests include formulation approaches for effective wound healing, colon-targeted drug delivery systems, and nanotechnology-based drug delivery systems for the transdermal and mucosal routes. Her team is currently working on surface-engineered polymeric nanoparticles for brain targeting and cancer therapy. Dr. Momin has published several research papers in national and international journals with good impact factors and has patents based on nanotechnology in the pipeline. She has three books on pharmaceutics and pharmaceutical engineering to her credit. She has undertaken a number of industrial research projects.

She is a reviewer for reputable journals from Elsevier and Bentham. ■

## Canadian Chapter of the Controlled Release Society 2016 Symposium: From Drug Discovery to Health Outcomes

Scott Campbell,<sup>1</sup> Yufei Chen,<sup>2</sup> and Emmanuel A. Ho<sup>2</sup>



*Attendees listening attentively to the exciting scientific sessions.*



*Attendees networking during the opening reception.*

The CRS Canadian Local Chapter (CC-CRS) had yet another successful meeting in Vancouver, British Columbia, bringing in members from across the country. Held jointly with the Canadian Society for Pharmaceutical Sciences (CSPS), the annual symposium included numerous talks and poster presentations highlighting research associated with controlled release and the pharmaceutical industry, bringing together closely related research fields. The CC-CRS organized three of the most popular sessions at the conference, held our annual general meeting, and also recruited numerous new members, including some from outside Canada.

The conference started with a workshop focused on the innovation and management of modern pharmaceuticals. Speakers from GlaxoSmithKline, Johnson & Johnson, Pfizer, and other biotech companies were present to discuss new trends in drug discovery and development, novel delivery technologies for therapeutics, and the future direction of the pharmaceutical industry. This was an exciting daylong workshop that provided CC-CRS members with an invaluable learning opportunity and a better understanding of current and future delivery science technologies in Canada. Once the conference officially began, CC-CRS organized three exciting sessions. The first session, “Nanomedicines Become Personal: Opportunities and Challenges,” was co-chaired by Shyh-Dar Li (University of British Columbia) and Amy Lee (Arbutus Pharma). Invited speakers included Kullervo Hynynen (Sunnybrook Research Institute), who discussed image-guided focused ultrasound for targeted drug delivery; Gang Zheng (Ontario Cancer Institute), who discussed porphyrin nanotechnology; and Rui Xue Zhang (University of Toronto), who presented research related to polymer-based nanomedicines for improving chemotherapy. The co-chairs Shyh-Dar Li and Amy Lee also presented their work on multifunctional nanoparticles and nucleic acid based therapeutics, respectively. The theme of the second session was “Responsive Drug Delivery Systems,”

co-chaired by Marc Gauthier (Institut National de la Recherche Scientifique) and Todd Hoare (McMaster University). Excellent talks were given by Adah Almutairi (University of California, San Diego), who discussed the development of smart automated release systems; Richard Hoogenboom (Ghent University), who presented his research on poly(2-oxazoline) biomaterials in the context of drug delivery; and Marc Gauthier, who gave a great overview of his research program surrounding bio-hybrid therapeutics. The third session was focused on “Protein and Peptide Delivery” and was co-chaired by Brian Amsden (Queen's University) and Larry Unsworth (University of Alberta). Invited speakers included Heather Sheardown (McMaster University) on ocular drug delivery,

*continued*

<sup>1</sup> McMaster University, Hamilton, ON, Canada.

<sup>2</sup> University of Manitoba, Winnipeg, MB, Canada.





*Attendees visiting the CRS booth.*

Boris Stoeber (University of British Columbia) on hollow metallic microneedles for intradermal delivery, Xiao Yu (Shirley) Wu (University of Toronto) on the application of bioinspired and nanotechnology-enabled therapeutics for diabetes and diseases in the brain, and co-chair Brian Amsden on new strategies for protein delivery from degradable microspheres. These sessions brought in top academic speakers from not only across Canada but also from around the world, including the Netherlands, Belgium, and the United States. There were also two oral presentations by trainees selected based on their highly ranked abstract submissions: Roy van der Meel (Utrecht University/University of British Columbia) on the use of polymeric micelles for targeted delivery of paclitaxel and Yannick Traore (University of Manitoba) on the development of an intravaginal ring for the combination delivery of therapeutics as a novel strategy for preventing HIV. The other Abstract Award winners included Celine Jimenez (University of Manitoba), Scott Campbell (McMaster University), and Sarandeep Malhi (University of Manitoba).

One of the major highlights of the conference was the poster session. This provided trainees from across Canada an opportunity to discuss and highlight the innovative controlled release-based research happening throughout the country. CC-CRS sponsored three poster awards for the best poster presentation at the conference. The winners of this year's competition were Hoda Soleymani (University of Alberta), Wei-Lun Tang (University of British Columbia), and Sidi Yang (University of Manitoba). Congratulations to these outstanding students.

During the annual general meeting, CC-CRS took the opportunity to highlight the current achievements of our organization, our financial situation, and our goals for the upcoming year, namely, the desire to expand our presence in Eastern Canada. Given the immense size of Canada, we hope to hold local regional events to build new local collaborations and to ensure that controlled release science is active and flourishing across the country. With that said, it has been a great year for CC-CRS. Membership within our chapter has increased by over 20% in the past year!

Overall, the three-and-a-half-day symposium was a great success. Not only were we able to fit in great science with networking opportunities, there was also an excellent banquet that allowed CC-CRS members to simply unwind and chat with friends—old and new. We invite everybody to join us at next year's annual symposium, to be held again in collaboration with CSPS in Montreal, Quebec (May 10–13, 2017). For more information regarding the annual symposium and local events in the upcoming year, please visit our website: <http://cc-crs.com>. ■



*CC-CRS President Emmanuel Ho presenting the Best Poster Presentation Award (left to right): Hoda Soleymani, Wei-Lun Tang, Sidi Yang, and Emmanuel Ho.*



*CC-CRS President Emmanuel Ho presenting the Best Abstract Award (left to right): Sarandeep Malhi, Celine Jimenez, Emmanuel Ho, Yannick Traore, Roy van der Meel, and Scott Campbell.*



# Joint Australian and New Zealand CRS Workshop

*Nicole Bisset, Monash Institute of Pharmaceutical Sciences, Monash University, Australia*

On April 21 and 22, 2016, Monash Institute of Pharmaceutical Sciences (MIPS) in Melbourne hosted the 2016 Joint Annual Australian–New Zealand CRS Student Workshop under the theme “Crossing Biological Barriers.” The workshop was the ninth in the series, which is held free of charge each year for students to attend. It was well attended, with approximately 100 attendees across the two days. Attendees came from Monash University, Melbourne University, RMIT, Swinburne, University of Newcastle, University of Queensland, University of Wollongong, University of New South Wales, University of Adelaide, and University of South Australia, as well as several students and academics from New Zealand institutions, including the University of Auckland and the University of Otago.

The aim of the workshop was to provide an overview and contemporary perspective of the issues around crossing biological barriers for advanced drug delivery across the area of tumour targeting, oral delivery, crossing the gastrointestinal tract, and transdermal delivery. To start the workshop, the chair of the organising committee, Ben Boyd (MIPS), welcomed delegates and introduced the following format of the workshop. The invited speakers were separated into related areas; there were two presentations per session, followed by 20 minutes for further discussion and questions. This format allowed students to engage with the presenters while providing a supportive environment that encouraged students to ask questions.

Day 1 was off to a great start with the session on tumour targeting, with our plenary speaker David Grainger (University of Utah, U.S.A.), presenting on “Bridging Realities: Perceptions and Barriers in Nanoparticle-Mediated Drug Delivery,” followed by Zach Houston (University of Queensland). Much interrogation of Prof. Grainger’s thesis followed in a lively discussion session. After lunch, Chris Porter (MIPS) and Mariusz Skwarczynski (University of Queensland) gave their perspectives on overcoming challenges with oral delivery of problematic drugs. The program on day 1 was completed with a final session on pulmonary (David Morton, Monash) and transdermal delivery (Mike Roberts, University of South Australia/University of Queensland).

The day was wrapped up a student-run trivia night for a fun evening of networking and socialising.



*Zach Houston finishes his presentation in front of the magnificent [Sissons Mural](#) at Monash Parkville campus.*



*Igor Chektman, a Ph.D. student at MIPS, chairs the oral drug delivery discussion session.*



*Tim Barnes attempts the impossible during the fun trivia social evening.*

*continued*



Day 2 started with a session on crossing the blood-brain barrier (Shakila Rizwan, University of Otago) and ocular drug delivery (Ilva Rupenthal, University of Auckland). Down at the cellular level, Angus Johnston (MIPS) described latest research into intracellular delivery of nanoparticles, while Colin Pouton (MIPS) discussed nuclear localization as a final hurdle in crossing biological barriers for genetic drugs. The final session of the workshop comprised a presentation by Cam Nowell (MIPS), who used fascinating images and videos to highlight how we can use imaging techniques to study the movement of small molecules and nanoparticles across biological barriers, and an industry perspective on hyphenated techniques from Scott Fraser (Perkin Elmer).

This workshop also saw the presentation of the Young Scientist Travel Award sponsored by ATA Scientific (AUD \$2000), to support travel to the CRS Annual Meeting. Ph.D. students were invited to submit a 400-word abstract that they would present at the meeting. The Australian CRS committee is grateful to the chair of the CRS Young Scientist Committee, David Chen, for his assistance in assessing the applications based on their novelty and technical clarity. The top three abstracts selected by Dr. Chen presented an eight-minute oral presentation on their work (followed by a two-minute question time). All three presentations were of high calibre; however, a panel of judges awarded the bursary to Lisa Belfiore (University of Wollongong). Congratulations! Lisa will present her work at the 2017 CRS annual meeting in Boston.



*Ilva Rupenthal discusses limitations in ocular drug delivery.*



*Angus Johnston and Colin Pouton engage the audience during the discussion session on cellular delivery.*



*Lisa Belfiore accepts the ATA Student Travel bursary for best student abstract and presentation from Ben Boyd.*



*Linda Hong (MIPS) accepts the runner-up prize for her presentation from Ben Boyd.*



*Nisa Abdul Ghaffir (University of Queensland) accepts the runner-up prize for her presentation from Ben Boyd.*

The organising committee would also like to take this opportunity to acknowledge and thank the sponsors of the workshop: ATA Scientific, the ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Perkin Elmer, the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, and the CRS Australian Local Chapter. These meetings don't happen without the support of external groups, particularly given that Ph.D. students could attend for free. Thanks also to the local organising committee, led by Lisa Kaminskis and Nicole Bisset, for a well-run and insightful workshop. Finally, thanks to the Australian and New Zealand committee members for their support of the event, as well as the financial support of the CRS for these important local chapter events. ■





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## People in the News

*Compiled by Steven Giannos, University of Texas Medical Branch, Galveston, TX, U.S.A.*

### **Wolfe Laboratories Addresses Rapid Growth with Executive Appointment**

Business Wire: June 14, 2016 – WOBURN, MA, U.S.A. – Wolfe Laboratories today announced that Frank Tagliaferri, PhD, has been appointed vice president, pharmaceutical development, effective immediately. Dr. Tagliaferri will lead technical operations for Wolfe's rapidly growing client base, bringing a wealth of experience in analytical methodologies, formulation and process development, scale-up, and regulatory functions across highly diverse therapeutic modalities, including small molecules, peptides, proteins, and nucleic acid therapeutics. Dr. Tagliaferri will serve as a member of Wolfe's executive leadership team and will report to Janet Wolfe, the company's president and chief executive officer.

"Frank's proven track record of success in developing and commercializing a broad range of novel therapeutics and dosage forms is essential to Wolfe Laboratories as we grow to meet increased client demand for a strong pharmaceutical development CRO partner," said Dr. Janet Wolfe. "I am thrilled to have the opportunity to work with Frank; he brings outstanding strategic leadership and technical acumen that will greatly benefit our clients' programs and overall company growth."

Most recently, Dr. Tagliaferri co-founded and served as vice president of R&D at 4P Therapeutics with a focus on the design, characterization, and commercial development of novel delivery systems and drug/device combination products for biologics and other complex molecules. Prior to joining 4P Therapeutics in 2012, Dr. Tagliaferri served as vice president of R&D for Altea Therapeutics, where he contributed to the development of the PassPort® system for the transdermal delivery of small molecules and biologics. Dr. Tagliaferri began his career at GeneMedicine (later Valentis, Inc.) where, as director of drug delivery, his focus was on the development and characterization of delivery systems for both DNA and proteins. He later served the same role at Tapestry Pharmaceuticals, working on small molecule anticancer agents and novel RNA-based therapeutics.

"Wolfe Laboratories' integrated pharmaceutical development services are making a meaningful difference for advancing pipelines at its clients' companies," said Dr. Frank Tagliaferri. "I'm excited to join an outstanding team and help Wolfe Laboratories leverage its sophisticated development expertise."

Dr. Tagliaferri earned his PhD in chemistry from the University of Virginia and a BA in chemistry from Franklin and Marshall College. He was a postdoctoral fellow at the University of Tennessee. ■



## Companies in the News

*Compiled by Steven Giannos, University of Texas Medical Branch, Galveston, TX, U.S.A.*

### July

#### **Shasqi Local Drug Activation Technology Provides Improved Drug Efficacy with Minimal Side Effects**

PRNewswire: July 20, 2016 – SAN FRANCISCO, CA, U.S.A. – Scientists at Shasqi, Inc. and SUNY University at Albany have published research demonstrating a way to target drugs to specific areas of the body, enabling greater efficacy and fewer side effects. The method, called local drug activation, uses activating agents in an injected polymer gel to concentrate and activate prodrug versions of a drug, such as a chemotherapeutic, directly at a desired location, limiting the drug's action to that specific site.

Their research shows that the local drug activation technology can deliver the chemotherapeutic drug doxorubicin directly to cancerous sarcoma cells in mice, eliminating the tumors while reducing the undesirable side effects commonly associated with chemotherapy. Moreover, while both traditionally delivered doxorubicin and the new delivery approach had an initial anticancer effect on the mice's sarcoma tumors, only the site-activated drug kept the cancer from returning. Sarcoma is an aggressive form of cancer that's responsible for up to 20% of childhood cancers. Surgery is often the primary treatment because traditional methods of chemotherapy are ineffective.

"During medical training it was frustrating to know that more than 97% of the medication that we give to patients never reaches its intended target. Whether the drug is ibuprofen or a chemotherapeutic, most of the medication is wasted, leading to side effects," said José M. Mejía Oneto, MD, PhD, president and chief executive officer of Shasqi, lead author of the new publication. "We believe that better methods of delivering drugs in the body will greatly improve the treatment of conditions where the desired site of action is well known by the physician and patient. This new research validates our approach in a challenging medical area of significant unmet need."

In addition to the greater efficacy and lack of tumor recurrence, mice treated using the local activation strategy had fewer side effects that can limit the use of combinations of cancer drugs. In particular, the researchers did not observe a decrease of new red blood cells, a marker of bone marrow suppression, which limits the tolerable dose of doxorubicin in patients. Other unpleasant side effects, such as weight loss, were not observed compared to those mice treated conventionally. The researchers plan to investigate whether shorter courses of therapy using higher doses of the chemotherapeutic can be even more effective and to expand this approach to other drugs and types of tumors.

"This drug targeting method is independent of molecular markers and allows drugs to be activated at a specific location for multiple weeks after the initial preimplantation of the gel at the desired treatment site," commented Dr. Mejía Oneto. "Because it protects healthy cells, including immune system cells, this approach may allow the concurrent use of multiple cytotoxic drugs or immunotherapies."

Shasqi is a privately held biopharmaceutical company, based in San Francisco, California. The company develops novel chemistry to optimize the healing power of modern medicine. Shasqi is backed by the National Science Foundation, the National Institutes of Health, and Y-Combinator. For more information, please visit our website at [www.shasqi.com](http://www.shasqi.com).

#### **Lannett Announces Receipt of FDA Acceptable Filing Letter for Fentanyl Patch ANDA**

PRNewswire: July 20, 2016 – PHILADELPHIA, PA, U.S.A. – Lannett Company, Inc. (NYSE: LCI) today announced that its strategic partner, Sparsha Pharma USA, Inc., has received an acceptable for filing letter from the U.S. Food and Drug Administration (FDA) of its Abbreviated New Drug Application (ANDA) for fentanyl transdermal system, 12, 25, 50, 75, and 100 mcg/hour, the generic equivalent of Ortho McNeil's chronic pain treatment Duragesic®. According to IMS, total U.S. sales in 2015 of fentanyl transdermal system products at average wholesale price (AWP) were more than \$650 million.

"Expanding our pain management franchise is a key component of our growth strategy," said Arthur Bedrosian, chief executive officer of Lannett. "Under the agreement, Sparsha Pharma USA will manufacture the product, and Lannett will be responsible for distribution. This alliance complements our Cody Labs active pharmaceutical ingredients (APIs) manufacturing operations and further supports and advances our plans for vertical integration."

Sparsha Pharma USA, founded in 2012, is a pharmaceutical company that specializes in research, development, and manufacture of transdermal therapeutic systems. Sparsha Pharma USA is committed to advancing patient care throughout the world by providing high quality and affordable transdermal drug delivery product lines.

Lannett Company, founded in 1942, develops, manufactures, packages, markets, and distributes generic pharmaceutical products for a wide range of medical indications. For more information, visit the company's website at [www.lannett.com](http://www.lannett.com).

### **STENTYS Enrolls First Patient in Left Main Clinical Trial**

Business Wire: July 19, 2016 – PRINCETON, NJ, U.S.A., and PARIS, France – STENTYS (Paris: STNT) (FR0010949404 — STNT), a medical technology company commercializing the world's first and only Self-Apposing® coronary stent, today announced that it has commenced enrolling patients in the TRUNC trial, which is designed to evaluate the long-term safety and efficacy of the Xposition S stent in the treatment of unprotected left main coronary artery disease.

The first implantation was performed at Treant hospital in Emmen, the Netherlands. Dr. Rutger Anthonio and Dr. Gillian Jessurun commented, "The procedure went very smoothly. The Xposition S stent is perfectly suited for the treatment of left main lesions, because it guarantees excellent apposition in a vessel segment with substantial diameter variation. In addition, the stent allows easy access to any anatomical side branch without the need to perform kissing balloon inflation, which minimizes overall manipulation."

Christophe Lottin, chief executive officer of STENTYS, added, "We are delighted by the start of this study, as left main interventions account for nearly 10% of PCI. We are aiming to demonstrate that the unique properties of our Self-Apposing technology make it the most optimal treatment for this complex indication."

TRUNC is a prospective, single-arm, multi-center trial to evaluate the long-term safety and efficacy of the Xposition S stent in the treatment of unprotected left main lesions in routine clinical practice. It is scheduled to include 200 patients in approximately 20 European clinical sites. The primary endpoint is target lesion failure at 12 months. The trial's steering committee is composed of Prof. Tamburino and Dr. Briguori (Italy) and Dr. Baumbach (U.K.).

STENTYS is developing and commercializing innovative solutions for the treatment of patients with complex artery disease. STENTYS's Self-Apposing® drug-eluting stents are designed to adapt to vessels with ambiguous or fluctuating diameters in order to prevent the malapposition problems associated with conventional stents. The APPPOSITION clinical trials in the treatment of acute myocardial infarction showed a very low one-year mortality rate and a faster arterial healing compared to conventional stents. The company's product portfolio also includes MiStent SES®, a coronary DES whose new drug delivery mechanism is designed to match vessel response, and is marketed through STENTYS's commercial network in Europe, the Middle East, Asia, and Latin America.

### **AngioSoma's Corporate Focus**

Business Wire: July 14, 2016 – MONTGOMERY, TX, U.S.A. – AngioSoma, Inc. (OTCQB: SOAN), previously known as First Titan Corp. (the "company," "we," and "our"), changed our corporate name and focus to that of a clinical-stage biopharmaceutical company, introducing an exciting new treatment for one of the world's most insidious and pervasive diseases, peripheral artery disease (PAD). The introduction of this new drug, Liprostin™, a liposomal controlled release encapsulation of prostaglandinE1 (PGE1), will greatly improve the effectiveness of the drug and of current standard-of-care treatments, especially when used with endovascular interventions such as transluminal percutaneous angioplasty, stenting, and atherectomy interventions in the treatment of PAD. The company's strengths include our research team, flagship product Liprostin™, intellectual property pipeline, and legacy oil and gas assets.

Our research team, headed by chairman emeritus Dr. David P. Summers, PhD, is a multi-talented, seasoned collection of applied scientists and medical field specialists assembled to produce product and market results—"this isn't their first rodeo!" Dr. Summers's biotechnical experience as both an engineer and biotechnical scientist bringing intellectual property to market is extensive, spanning multiple decades. "Working with Dr. Summers is an absolute pleasure! His long history of leading research teams from product and technology conceptualization, through product development, and then to product sales is amazing," said Alex Blankenship, AngioSoma, Inc.'s CEO.

Liprostin™, our flagship product, is an FDA-approved product in a new controlled delivery system, a sterically stable liposome that has made our product, the well-known generic prostaglandinE1 (PGE1), a brand new drug with a brand new controlled delivery. The Liprostin™ market is a very large multi-billion-dollar international market. There are many derivative treatments such as diabetes, peripheral neuropathies, and various vascular disorders that may be candidates for treatment once FDA approval is obtained, and information amassed by our research team will provide a continuous stream of intellectual property (IP), yielding future patent protection and future products.

Our intellectual property pipeline is large and has expired or expiring patents providing a basis for new product development, patent applications, and research, continually enlarging the pipeline and future products even further.

The company still owns assets in the oil and gas industry that may provide independent shareholder value in the future. We have already begun to explore various strategies to unlock this shareholder value while not detracting from our current focus.

AngioSoma, Inc. ([www.angiosoma.com](http://www.angiosoma.com)), a Nevada corporation based in Montgomery, Texas, is a clinical-stage biotechnology company focused on improving the effectiveness of current standard-of-care treatments, especially related to endovascular interventions in the treatment of peripheral artery disease (PAD). Our lead pharmaceutical product, Liprostin™, for the treatment of PAD, has successfully completed FDA phase I and three phase II clinical trials, and we are in discussions with several contract research organizations (CROs) for rapid completion of our U.S. Food and Drug Administration (FDA) approved protocol for phase III with submission of our new drug application (NDA) for marketing in the United States and its territories.

#### **TARIS Biomedical® Initiates Phase 1b Clinical Trial of TAR-200 (GemRIS™) in Patients with Muscle-Invasive Bladder Cancer**

Business Wire: July 13, 2016 – LEXINGTON, MA, U.S.A. – TARIS Biomedical LLC, a company developing powerful and targeted new treatments for millions of patients suffering from difficult-to-treat bladder diseases, announced today the initiation of a phase 1b clinical trial of TAR-200 (GemRIS™) in patients with muscle-invasive bladder cancer (MIBC). TAR-200, a drug-device combination product utilizing the TARIS® system, is designed to release gemcitabine continuously into the bladder over 7 days. TARIS® also announced that Christopher J. Cutie, MD, MBA, has been promoted to chief medical officer to oversee all of TARIS's clinical programs.

"Patients diagnosed with muscle-invasive bladder cancer often require complex treatment regimens, including systemic chemotherapy and radical cystectomy (complete surgical removal of the urinary bladder), a life-altering operation associated with significant morbidity and, in some cases, death. Unfortunately, one or both of these treatments are not suitable for many patients suffering from this potentially lethal disease," said Dr. Cutie. "TAR-200 has the potential to address patients underserved by the current standard of care."

"To our knowledge, this is the first time any drug has ever been continuously delivered into the bladder to treat a bladder tumor over such an extended period. We are excited about this novel treatment approach and look forward to seeing the results of this study," said Purnanand Sarma, PhD, president and chief executive officer of TARIS. "Launching our first clinical trial in oncology is a significant milestone for TARIS. Building on the momentum from our Allergan transaction announced in 2014, we are rapidly expanding the organization and plan to move multiple programs into the clinic in the coming 12–18 months. We are pleased to recognize Dr. Cutie's superb leadership of our clinical programs with his promotion to chief medical officer."

The phase 1b open-label study will assess whether continuous, local exposure to gemcitabine using TAR-200 is safe and tolerable in patients with MIBC. The study will also assess the preliminary efficacy in this patient population. The study will be conducted at multiple sites in the United States and expects to enroll up to 20 patients after the diagnosis of MIBC and before radical cystectomy.

TAR-200 (GemRIS™) is TARIS's first program in bladder cancer. TAR-200 is a drug-device combination product designed to release gemcitabine continuously into the bladder over 7 days. Gemcitabine is commonly used to treat multiple cancers alone and in combination with other chemotherapeutic drugs. TARIS believes TAR-200 has the potential to set a new standard of care in bladder cancer, with enhanced efficacy and minimal systemic side effects compared to current approaches. TARIS is developing TAR-200 to address unmet needs in both muscle invasive and non-muscle invasive bladder cancer.

Bladder cancer affects roughly 2.7 million people worldwide, including nearly 600,000 in the United States. The National Cancer Institute estimates that there will be a total of nearly 77,000 new cases and 16,000 deaths due to this disease in 2016. When measured as a cumulative lifetime per patient cost, the expense to treat bladder cancer exceeds all other forms of cancer. The estimated U.S. national expenditure on bladder cancer was \$4.3 billion in 2014.

Muscle invasive bladder cancer (MIBC) is an advanced form of the disease, representing 25–30% of the newly diagnosed cases. MIBC tumors, which have progressed into the muscle of the bladder wall and potentially beyond, may lead to metastases and death. The standard of care for treatment of MIBC includes radical cystectomy, or complete removal of the bladder, with or without neoadjuvant chemotherapy. Radical cystectomy is a major, life-changing procedure, and many patients are medically unfit and/or unwilling to undergo the procedure.

The TARIS® system is a controlled release dosage form for use in the bladder. The system uses passive delivery principles to continuously release drug in the bladder over weeks to months. It is deployed into and retrieved from the bladder using minimally invasive in-office procedures. This technology allows drug release to be tailored to match the needs of specific treatment regimens.

TARIS Biomedical® is building a unique therapeutically focused urology company developing powerful and targeted new treatments for millions of patients suffering from difficult-to-treat bladder diseases. We are advancing therapies for debilitating conditions, including bladder cancer and overactive bladder, enabled by continuous local dosing where it is needed. [www.tarisbiomedical.com](http://www.tarisbiomedical.com).

### **Aphios Awarded Subcontract for Nanoformulation of Superhydrophobic Anticancer Drug**

Business Wire: July 12, 2016 – WOBURN, MA, U.S.A. – Aphios Corporation announced today that it has been awarded a subcontract for the nanoformulation of a superhydrophobic anticancer drug administered through the Frederick National Laboratory for Cancer Research in Frederick, Maryland.

Several promising natural products being developed as the active pharmaceutical ingredients of investigational drug products have encountered roadblocks that nanotechnology may be able to address. One of these promising anticancer drugs is brefeldin A (BFA), a cyclic macrolide with a lactone ring. BFA has demonstrated potent activities in controlling protein trafficking, signal transduction cycles, and apoptosis. However, clinical development of this promising anticancer drug has been halted because of the inability to develop an intravenous formulation of this water-insoluble, highly hydrophobic active pharmaceutical ingredient.

The primary goal of this research program is to pair brefeldin A (BFA) with Aphios's SuperFluids™ critical fluid nanosomes (SFS-CFN) technology for intravenous administration to achieve and maintain therapeutic plasma concentrations. The nanoBFA IV research is being funded via a research subcontract from Leidos Biomedical Research, Inc., prime contractor for the Frederick National Lab, sponsored by the National Cancer Institute.

Dr. Trevor P. Castor, principal investigator of the subcontract, states, "Our rationale for pairing BFA with SFS-CFN technology is that BFA is highly hydrophobic and insoluble in water. As such, during the encapsulation process, BFA will be sequestered in the lipid bilayer of phospholipid nanosomes, making an aqueous-based nanoformulation of this water-insoluble drug. This process is very similar to one that we have developed for camptothecin (CPT), a highly hydrophobic and water-insoluble lactone, derivatives of which are approved by the FDA for colorectal, cervical, pancreatic, and other cancers. Aphios is also developing nanosomes of neat CPT, Camposomes™, to improve efficacy and reduce toxicity of this potent topoisomerase-1 inhibitor for pancreatic and other cancers."

Aphios ([www.aphios.com](http://www.aphios.com)) is a clinical-stage biotechnology company developing green enabling technology platforms to improve drug discovery, manufacturing, nanotechnology drug delivery, and pathogenic safety, and enhanced therapeutics to improve quality-of-life and treat chronic diseases such as prostate and pancreatic cancer, infectious diseases such as HIV, and central nervous system disorders such as Alzheimer's disease and multiple sclerosis in an environmentally sustainable manner.

### **SwRI, UTSA Invest in Two New Joint Biomaterial Research Projects**

Business Wire: July 6, 2016 – SAN ANTONIO, TX, U.S.A. – Southwest Research Institute (SwRI) and the University of Texas at San Antonio (UTSA) Office of the Vice President for Research announced two new research projects through the Connecting Through Research Partnerships (Connect) Program. The projects are slated to begin September 1, 2016, with each receiving \$125,000 in funding. The two projects will investigate biofilm corrosion in pipelines and an ultrasound drug delivery methodology.

"These joint UTSA and SwRI programs leverage talent at both organizations, build strong teams for future contract opportunities, and accelerate the transition of fundamental research to the public," said Dr. Michael MacNaughton, vice president of the SwRI Chemistry and Chemical Engineering Division.

Biofilms often cause microbiologically influenced corrosion (MIC) and are a serious problem in pipelines and other infrastructure. SwRI and UTSA will collaborate to gain a better understanding of MIC by collecting genomic and metabolic data from biofilms. These data will be used to develop models that can predict corrosion and identify potential novel inhibitors of biofilm formation. This research is geared toward the petroleum industry where problematic biofilms occur in many of the production and distribution processes. However, it has broad implications in other pipeline industries as well as medical applications where dental and other types of implants are used.

Manager Dr. Tony Reeves, principal scientist Dr. Kennedy Gauger, and scientist Kenneth Lange, all of SwRI's Pharmaceuticals and Bioengineering Department, will collaborate with UTSA College of Engineering researcher Dr. Heather Shipley, chair of the Civil



and Environmental Engineering Department, and Dr. Gisella Lamas-Samanamud, a postdoctoral fellow, on the project “Molecular Characterization and Quorum Sensing of Microbiologically Influenced Corrosion (MIC) in Pipeline Populations.”

Precision medicine, also called personalized medicine, takes the approach that no one treatment fits all patients, tailoring medical decisions by considering the predicted response of an individual. Together UTSA and SwRI will explore new ways to monitor a drug once it has been given *in vivo*. The team will develop a new approach using acoustic-sensitive liposomes for ultrasound-mediated drug release and then monitor the real-time drug concentrations in deep tissue.

Staff engineer Dr. Jian Ling of SwRI's Pharmaceuticals and Bioengineering Department and UTSA's Dr. Jing Yong Ye will collaborate on “Ultrasound Mediated Drug Delivery in 3D Tissue Model Quantified by Photoacoustic Tomography.” Ye is the interim department chair of biomedical engineering in the UTSA College of Engineering.

“The ability to control the release of therapeutics in targeted tissues with a desired spatial distribution and at an adjustable rate according to the drug response of each individual is important for personalized medicine,” Ling said.

Over the past six years, 11 projects have been funded under the joint SwRI-UTSA Connect Program.

“Fostering collaborative opportunities for researchers from our two institutions has led to scientific discoveries and advanced technologies. The Connect Program continues to surpass our expectations. These two projects focus on priority funding areas—biomaterials and biomedicine. Together we are finding new ways to address these difficult technical challenges,” said SwRI executive vice president Walt Downing.

“When we leverage the research expertise of both institutions and cross-pollinate efforts through the Connect Program, we can spark innovation and progress,” said Dr. Bernard Arulanandam, UTSA interim vice president for research. “Our funding selection committee is looking to fund research that finds solutions for specific challenges. This year, with the two chosen projects—precision medicine and pipe corrosion in the petroleum industry—we can have a systemic impact on the people, and the industries, of Texas.”

The Connect Program was founded to enhance scientific collaboration between SwRI and UTSA and increase their research funding base.

#### **Transdermal Delivery Solutions and MHC Medical Products Announce License for Penetran Plus® Topical Pain Reliever**

Business Wire: July 5, 2016 – PALM BEACH GARDENS, FL, U.S.A. – Transdermal Delivery Solutions Corporation (TDSC), [www.TDSC.us](http://www.TDSC.us), announced today the signing of a product license arrangement with MHC Medical Products, LLC of Cincinnati, Ohio.

“We are pleased to announce the finalization of our agreement for this first product with the team at MHC,” said Kenneth Kirby, president of TDSC. “MHC is the manufacturer of one of the country’s fastest growing lines of branded medical devices and other consumer healthcare products, including the EasyTouch® brand of insulin syringes and blood glucose meters, HealthPro® blood glucose meters, and SureLife® blood pressure monitors.” With the acquisition of Penetran Plus®, MHC is expanding into the over-the-counter pain relief market.

Up until this time, Penetran Plus had limited regional distribution. “We are pleased and honored to have the MHC team acquire the product license and expand the distribution,” said Kirby. Penetran Plus is a topical analgesic gel that is marketed as an over-the-counter remedy for temporary relief of minor aches and pains, bruises, and strains. The product was designed with a pleasant natural lemon oil fragrance, a nonsticky formula, and has been successfully tested for pains associated with arthritis in a double-blind study against placebo, which was published in a peer-reviewed journal. The product label has been reviewed by the FDA Center for Drug Evaluation and Research Office of Unapproved Drugs and Labeling Compliance (OUDLC), Over the Counter Branch, and found to be in compliance with the OTC Monograph for Topical Pain Relief.

TDSC is committed to advancing the science of transdermal drug delivery using its patented spray-on delivery system. TDSC’s proprietary system enables medications to be delivered directly through the skin, for systemic or localized application, utilizing its rapid-acting, patchless, spray-on technology. The company’s technology is flexible enough to be applicable to a very wide range of compounds up to small peptides for pharmaceutical or cosmetic use. No other company can offer similar, consumer friendly, dosing-flexible solutions. [www.youtube.com/watch?v=Ff-1z1SYoF8](http://www.youtube.com/watch?v=Ff-1z1SYoF8).

## June

### **Gecko Biomedical Receives 1.4 Million Euros in Interest-Free Loan from Bpifrance to Advance Its Bio-Inspired Surgical Adhesive Solutions**

Business Wire: June 30, 2016 – PARIS, France – Gecko Biomedical (“Gecko”), a French medical device company developing innovative polymers to support tissue healing, announced today that it has received an interest-free loan of 1.4 million euros from Bpifrance to advance its bio-inspired surgical adhesive solutions.

These funds will be dedicated to supporting Gecko Biomedical clinical trials in Europe in order to obtain CE Mark in the first half of 2017.

The funds are part of Bpifrance’s support of innovation through its interest-free loan program (Prêt à Taux Zéro pour l’Innovation–PTZI), providing repayable advances to encourage the development of innovative products.

Christophe Bancel, Gecko Biomedical’s chief executive officer, said, “Bpifrance’s continuous support not only provides us with financial stability towards our future, but also is a testimony of the value of our biopolymers platform. As such, Bpifrance is a central stakeholder to our short, medium, and long-term development.”

Gecko Biomedical is a privately owned medical device company based in Paris, France, that is dedicated to the rapid development and commercialization of a unique biopolymers platform. Gecko’s first product (GB-02) is an innovative polymer for tissue healing, targeting cardiovascular reconstruction as an initial indication. The structure of GB-02 is tunable, allowing customization for various applications and tissues. Gecko’s biopolymers platform is fully industrialized and highly versatile, with potential novel applications in other fields of tissue reconstruction, such as guided tissue repair and localized drug delivery.

Gecko’s platform is based on proprietary biopolymers with unique chemical and physical properties, including high viscosity, hydrophobicity and fast “on demand” curing for precise local delivery and *in situ* adhesion. The company’s technologies are derived from world-class research and intellectual property from the laboratories of Prof. Robert Langer (MIT) and Prof. Jeff Karp (Brigham and Women’s Hospital), who co-founded the company in 2013, alongside Christophe Bancel and Bernard Gilly from the iBionext Network. For more information, please visit [www.geckobiomedical.com](http://www.geckobiomedical.com) and follow [@geckobiomedical](https://twitter.com/geckobiomedical).

Bpifrance, a subsidiary of Caisse des Dépôts and the French State, is a trusted partner of entrepreneurs that provides companies with credit, collateral, and equity financing support from start up through to stock exchange listing. Bpifrance also provides guidance services and enhanced support for innovation, external growth, and export, in partnership with Business France and Coface.

Bpifrance offers companies a continuum of financing for each key stage of their development and an offer adapted to specific regional features. With 42 regional offices (90% of decisions are made regionally), Bpifrance offers entrepreneurs a tool for economic competitiveness. Bpifrance works in support of the public policies pursued nationally and regionally by the French government, to meet three objectives:

- support the growth of businesses;
- prepare for future competitiveness;
- contribute to the development of a favorable ecosystem for entrepreneurship.

With Bpifrance, companies have a strong and effective local contact to meet all their financial, innovation and investment needs. For more information, please visit [www.bpifrance.fr](http://www.bpifrance.fr), <http://investissementsdavenir.bpifrance.fr/>, Twitter: [@bpifrance](https://twitter.com/bpifrance).

### **New Preclinical Data Show Potential of Dicerna GalXC™ Subcutaneous Delivery Platform as RNAi Drug Discovery Engine**

Business Wire: June 29, 2016 – CAMBRIDGE, MA, U.S.A. – Dicerna Pharmaceuticals, Inc. (NASDAQ: DRNA), a leading developer of investigational RNA interference (RNAi) therapeutics, today will unveil preclinical data showing the promise of its proprietary GalXC™ subcutaneous (SC) delivery platform as an RNAi drug discovery engine. At the company’s Investor Day conference in New York City, Dicerna management will present preclinical data both from nonhuman primates and from rodent disease models showing that GalXC enables direct delivery of RNAi-based therapy to the liver via SC injection, with potential utility against diverse therapeutic targets, based on consistent, potent, and durable silencing of multiple disease-causing genes in the liver.

“The GalXC platform significantly strengthens our capabilities to develop next-generation RNAi-based therapies that silence disease-driving genes in the liver. Evidence presented today spans GalXC conjugates in various states of optimization targeting a dozen gene targets implicated in various rare diseases, chronic liver diseases, cardiovascular disease, and hepatitis B virus,” said Douglas Fambrough, PhD, president and chief executive officer of Dicerna. “We expect to file an investigational new drug application for our first GalXC therapy in late 2017. We also anticipate identifying three clinical candidates annually starting in 2016, both on our own and potentially in collaboration with development partners.”

At the Investor Day conference, Dicerna will report on the preclinical application of GalXC RNA duplexes to achieve gene silencing of well-characterized hepatic disease genes such as HAO1, Alpha-1-antitrypsin (SERPINA1), and numerous undisclosed targets, as well as updated tolerability data, molecular details of the GalXC platform, and the history of GalNAc-mediated delivery of oligonucleotides to the liver. Use of the GalXC platform has yielded gene silencing of greater than 90% for multiple genes in nonhuman primates after a single dose. In a nonhuman primate experiment, the maximum HAO1 gene silencing after a single 3 mg/kg dose was 94%, with an average gene silencing of approximately 88%. Another single 3 mg/kg dose nonhuman primate study resulted in an average of 97% silencing of an undisclosed rare disease gene target. Duration of effect data suggest a monthly preclinical dosing interval, or even less frequently for select gene targets.

The GalXC platform relies on Dicerna’s GalNAc DsiRNA-EX conjugate technology platform to deliver RNAi therapies by SC administration. Dicerna scientists attach small drug delivery agents, known as N-acetylgalactosamine (GalNAc) sugars, directly to the extended region of a Dicer substrate short-interfering RNA (DsiRNA-EX) molecule, a chemically optimized, double-stranded RNA developed by Dicerna. The GalNAc sugars specifically bind to receptors on target cells in the liver, leading to effective delivery and silencing of specific gene targets within the cells. Many of the conjugates produced using the GalXC platform incorporate a folded motif known as a tetraloop, which stabilizes the RNA duplex and provides multiple conjugation points for the addition of GalNAc sugars. The tetraloop configuration, which is unique to Dicerna’s conjugates, interfaces effectively with the RNAi machinery within target cells.

“The longer RNAi duplexes of our GalXC molecules provide greater flexibility to enhance their pharmaceutical properties, including increased potency and reduced toxicity,” explained Bob D. Brown, PhD, chief scientific officer and senior vice president of research at Dicerna. “The GalXC platform allows us to screen and optimize therapeutic leads in mice and monkeys with remarkable efficiency. Within a month of nominating a gene target expressed in the liver, we are able to design, synthesize, and validate GalXC duplexes in animal models.”

GalXC™ is a proprietary technology platform invented by Dicerna to advance the evaluation of next-generation RNAi-based therapies designed to silence disease-driving genes in the liver. Compounds produced via the GalXC technology are intended to be broadly applicable across multiple therapeutic areas including cardiovascular disease, nonalcoholic steatohepatitis (NASH) and related fibrotic conditions of the liver, hepatitis B virus (HBV), and various rare diseases. Using GalXC, Dicerna scientists attach N-acetylgalactosamine (GalNAc) sugars directly to the extended region of a Dicer substrate short-interfering RNA (DsiRNA-EX) molecule, yielding multiple proprietary conjugate delivery configurations. GalXC enables subcutaneous delivery of Dicerna’s RNAi therapies to hepatocytes in the liver, where they are designed to specifically bind to receptors on target cells, potentially leading to internalization and access to the RNAi machinery within the cells. The technology may offer several distinct benefits, as suggested by robust preclinical data. These benefits include potent silencing of gene targets; highly specific binding to hepatocytes; long duration of action; and an infrequent subcutaneous dosing regimen, while retaining the potential for intravenous dosing, allowing for flexibility in mode of administration. Conjugates produced via the GalXC platform can be administered as simple saline solutions and do not need transport technologies (such as lipid nanoparticles) to facilitate delivery.

Dicerna Pharmaceuticals, Inc., is an RNA interference-based biopharmaceutical company focused on the discovery and development of innovative treatments for rare, inherited diseases involving the liver, for other therapeutic areas in which the liver plays a key role, and for cancers that are genetically defined. The company is using its proprietary RNA interference (RNAi) technology platform to build a broad pipeline in these therapeutic areas. In many cases, Dicerna is pursuing targets that have historically been difficult to inhibit using conventional approaches, but where connections between targets and diseases are well understood and documented. The company intends to discover, develop, and commercialize these novel therapeutics either on its own or in collaboration with pharmaceutical partners. For more information, please visit [www.dicerna.com](http://www.dicerna.com).

## **Acorda Presents Phase 1 Data on CVT-427 for Acute Treatment of Migraine at 58th Annual Scientific Meeting of the American Headache Society**

Business Wire: June 9, 2016 – ARDSLEY, NY, U.S.A. – Acorda Therapeutics, Inc. (Nasdaq: ACOR) today announced pharmacokinetic (PK) data from a phase 1 study of CVT-427, an inhaled formulation of zolmitriptan, resulting in increased bioavailability and faster absorption compared to oral and nasal administration of the same active ingredient in healthy adults. The data on CVT-427, an investigational agent under development for the acute treatment of migraines, will be presented on June 10, 2016, at the 58th Annual Scientific Meeting of the American Headache Society, in San Diego, California.

“When surveyed, the majority of migraine sufferers said rapid pain relief is one of the most important factors influencing their medication preference,” said Rick Batycky, PhD, Acorda Therapeutics’ chief technology officer. “We’re encouraged by the findings of this PK study, which support advancing development of CVT-427 for the acute treatment of migraine.”

This phase 1, open-label, inpatient, single ascending dose trial enrolled 21 healthy adults; 17 completed all treatments. Each subject first received successively, single doses of the zolmitriptan reference formulations, a 5 mg oral tablet, and a 5 mg nasal spray. Subjects then received four individual premeasured doses of CVT-427 (0.825 mg [0.6 mg delivered to the lung], 1.65 mg [1.2 mg], 3.0 mg [2.4 mg], and 6.0 mg [4.8 mg] of zolmitriptan). There was a one or two day washout period between each administration.

The oral and nasal spray formulations had a median T<sub>max</sub> of 1.5 hours and 3.0 hours, respectively; all four dose levels of CVT-427 had a median T<sub>max</sub> of 0.17 hours.

The mean C<sub>max</sub> for the oral formulation was 8.7 ng/mL, and the nasal spray formulation was 8.1 ng/mL. The mean C<sub>max</sub> values for CVT-427 were 6.0 ng/mL (0.825 mg dose), 11.8 ng/mL (1.65 mg), 17.8 ng/mL (3.0 mg), and 35.0 ng/mL (6.0 mg).

The mean AUC<sub>0-24</sub> (ng·hr/mL) values for the reference formulations were 49.0 for the oral and 50.8 for the nasal spray, whereas the mean AUC<sub>0-24</sub> values for CVT-427 were 14.7 (0.825 mg dose), 27.3 (1.65 mg), 47.1 (3.0 mg), and 91.0 (6.0 mg). Coefficient of variation for AUC<sub>0-24</sub> with reference products ranged from 37.6 to 38.4% compared with 26.7–29.9% for CVT-427, showing less variability.

PK parameters (including bioavailability) of the reference formulations observed in the trial matched published reports. The study found that CVT-427 had better bioavailability than the reference formulations with less variability in plasma concentration.

There were no serious adverse events, dose limiting toxicities, or study discontinuations due to adverse events (AEs) reported for CVT-427. The most commonly reported treatment-emergent AEs for CVT-427 (≥10%) were cough (0.825 mg – 11%, 1.65 mg – 11%, 3.0 mg – 22%, 6.0 mg – 18%), chest discomfort (0.825 mg – 11%), headache (1.65 mg – 11%), and feeling hot (3.0 mg – 11%, 6.0 mg – 24%). Other than cough, single dose CVT-427 tolerability was generally consistent with the known safety profile of zolmitriptan.

“Tolerability and Pharmacokinetics of Zolmitriptan Administered via CVT-427, a Novel Pulmonary Delivery System,” (Poster #PF72LB) was presented on Friday, June 10, 1:15–2:30pm Pacific Time. Herbert R. Henney III, PharmD, vice president, clinical pharmacology for Acorda, presented the poster. This study was supported by Acorda Therapeutics, Inc.

More detailed information on the meeting can be found on the conference website: <https://americanheadachesociety.org>.

CVT-427 is an inhaled formulation of zolmitriptan that uses the company’s proprietary ARCUS® technology. Zolmitriptan belongs to a class of drugs known as triptans, which are a leading therapy for acute treatment of migraines. An estimated 36 million people in the United States, and over 40 million people in Europe, suffer from migraines.

Acorda’s proprietary ARCUS technology platform is a dry-powder pulmonary delivery system that has potential applications in multiple disease areas. This platform allows consistent and precise delivery of significantly larger doses of medication than are possible with conventional pulmonary systems. The ARCUS inhaler is breath-actuated, operated by the user simply breathing in.

The ARCUS technology has been used to successfully deliver more than one million doses to patients in clinical trials of various products. There are currently two clinical-stage programs using the ARCUS technology: CVT-301 (phase 3) is in development as a treatment for symptoms of OFF periods in Parkinson’s disease; CVT-427 (phase 1) is in development for the acute treatment of migraines. Acorda has an extensive patent portfolio relating to CVT-301, CVT-427, and the ARCUS technology, which covers aspects of the formulated drug product, the inhaler, the method of drug delivery, and manufacturing processes.



Founded in 1995, Acorda Therapeutics is a biotechnology company focused on developing therapies that restore function and improve the lives of people with neurological disorders.

Acorda has an industry-leading pipeline of novel neurological therapies addressing a range of disorders, including Parkinson's disease, poststroke walking difficulties, migraine, and multiple sclerosis. Acorda markets three FDA-approved therapies, including AMPYRA® (dalfampridine) extended release tablets, 10 mg. For more information, please visit the company's website at [www.acorda.com](http://www.acorda.com).

### **Highland Therapeutics Announces Positive Data from Second Pivotal ADHD Trial for HLD-200**

Business Wire: June 6, 2016 – TORONTO, Canada – Highland Therapeutics Inc.'s wholly owned subsidiary, Ironshore Pharmaceuticals and Development, Inc. ("Ironshore"), today announced positive clinical data from the second phase 3 pivotal trial of its investigational drug product, HLD-200 (delayed-release and extended-release methylphenidate capsules). HLD-200, whose brand name has been provisionally accepted as Benjorna™, is under development as a potential new option for physicians treating patients with attention deficit hyperactivity disorder (ADHD). In the clinical study (HLD200-108), which included 161 pediatric patients (ages 6–12), the group randomized to receive HLD-200 achieved a 44% improvement in ADHD symptom scores, a highly statistically significant positive difference compared to the placebo group ( $p = 0.002$ ), based on the ADHD-RS-IV rating scale, the study's primary endpoint.

Commenting on the HLD200-108 results, Dr. Steven R. Pliszka, MD, professor and chair of the Department of Psychiatry of the University of Texas Health Science Center at San Antonio and an investigator in the study, said, "These data support our long-standing clinical hypothesis that HLD-200 may, if approved, become a particularly helpful new option for the many families that are struggling with uncontrolled symptoms of ADHD during the chaotic early morning routine. The novelty of Ironshore's approach—having a stimulant administered in the evening intended to treat ADHD symptoms the following morning and into the evening—would represent a new way for physicians to provide comprehensive therapeutic coverage for ADHD patients."

In the HLD200-108 trial, the group randomized to the treatment arm also achieved improved functioning scores during the morning routine as measured by two separate scales—each of which was designated as a key secondary endpoint. On the Before School Functioning Questionnaire (BSFQ), the treatment group achieved a 59% improvement in functioning compared with the average baseline score, a highly statistically significant difference relative to the placebo group ( $p < 0.001$ ). The BSFQ is a rating scale developed by clinicians at Massachusetts General Hospital's Division of Child and Adolescent Psychiatry that measures both behaviors and functions associated with the postwaking, early morning period in children and adolescents with ADHD. These include getting out of bed, getting dressed, hygiene, and getting to school.

With respect to the PREMB-R (Parent Rating of Evening and Morning Behavior–Revised) morning (AM) subscale, another key secondary endpoint, the treatment group showed a 66% improvement, compared with baseline, also a highly statistically significant result compared with the placebo group ( $p < 0.001$ ).

The treatment group also achieved a 44% improvement in functioning in the evening as measured by the PREMB-R evening (PM) subscale ( $p = 0.002$ , relative to the placebo group). These positive results, from the early morning through to the evening time period, have now been observed in three separate phase 3 trials—two of which were pivotal studies.

"The technical challenges associated with dosing a stimulant medication at bedtime to target an onset of meaningful clinical effect upon awakening were significant," said David Lickrish, president and chief executive officer. "Given what we now know about the critically important role that pharmacokinetics play in this therapeutic category, the results from this study, and the two phase 3 studies previously completed, give us increasing confidence that, if approved, HLD-200 will have the potential to displace older medications that rely on simple controlled-release technologies."

Dr. Randy Sallee, Ironshore's chief medical officer, stated, "It is gratifying to see consistent positive results in three separate clinical studies, which reflects the output of Ironshore's science-driven approach to drug development, a philosophy we have followed since the company was founded. As a practicing clinician for over 25 years, I believe HLD-200 will, if approved, provide a unique treatment option for patients, caregivers, and health care providers."

Initiated in 2015, the HLD200-108 trial was a phase III, multicenter, double-blind, randomized, placebo-controlled, parallel group study to evaluate the safety and efficacy of evening-dosed HLD-200 on postwaking, early morning function in children aged 6–12 with ADHD. The study randomized 161 patients at 22 centers across the United States.

Highland Therapeutics Inc. is a pharmaceutical company that, through its wholly owned subsidiary Ironshore Pharmaceuticals and Development, Inc., is leveraging its proprietary technology DELEXIS® to optimize the delivery of previously approved drug products. The company's lead product candidates, HLD-200 and HLD-100, are novel formulations of the psychostimulants (methylphenidate and amphetamine, respectively) used to treat ADHD and are being developed to address a prevalent unmet medical need in the treatment of the disease—inadequate symptom control during the morning routine. Intended for nighttime dosing, DELEXIS® is designed to provide a consistent delay in the initial release of the active drug, followed by a period of extended release, with the objective of providing control of ADHD symptoms immediately upon waking and throughout the day. The company is also leveraging DELEXIS® in investigational drug products targeting binge eating disorder (HLD-900) and inflammatory bowel disease (HLD-400).

Highland Therapeutics Inc. is a client of MaRS Discovery District's Health Venture Services group, which provides advisory services, connections to talent, customer, and capital networks, and market intelligence to high-impact, Ontario-based life sciences ventures, helping them commercialize their ideas and build globally competitive companies. For further information, please visit the company's website at [www.highlandtherapeutics.com](http://www.highlandtherapeutics.com).

## May

### **\$1.8 Million Fast-Track NIH SBIR Grant for Manocept™ Immunotherapeutics Evaluation in Kaposi's Sarcoma Awarded to Navidea**

Business Wire: May 26, 2016 – DUBLIN, OH, U.S.A. – Navidea Biopharmaceuticals, Inc. (NYSE MKT: NAVB) announced the receipt of an initial notice of award for a fast-track Small Business Innovation Research (SBIR) grant providing for up to \$1.8 million from the National Institutes of Health's (NIH's) National Cancer Institute (NCI) to fund evaluation of an investigational Manocept™-based immunotargeted treatment for Kaposi's sarcoma (KS). The novel Manocept construct is designed to specifically deliver doxorubicin, a chemotoxin, which can kill KS tumor cells and their tumor-associated macrophages (TAMs), potentially altering the course of cancer. KS is a serious and potentially life-threatening illness in persons infected with the human immunodeficiency virus (HIV) and the third-leading cause of death in this population worldwide. The prognosis for patients with KS is poor, with high probabilities for mortality and greatly diminished quality of life. The development activities of the Manocept immunotherapeutic platform will be conducted by Navidea and its subsidiary, Macrophage Therapeutics.

The funds for this fast-track grant (NCI of the NIH under Award Number R44CA206788) will be released in three parts, which together have the potential to provide up to \$1.8 million in resources over 2.5 years with the goal of completing an investigational new drug (IND) submission for a Manocept construct (MT1000 class of compounds) consisting of tilmanocept linked to doxorubicin for the treatment of KS. The first part of the grant will provide \$232,000 to support analyses including *in vitro* and cell culture studies and will be followed by part 2 and 3 animal testing studies. If successful, the information from these studies will be combined with other information in an IND application that will be submitted to the U.S. Food and Drug Administration (FDA) requesting permission to begin testing the compound selected in human KS patients.

"We believe that given the data to date from the Manocept platform, these studies along with a host of other human tumor model studies ongoing and planned for animal testing will provide a powerful gateway to a new class of anti-TAM immunotherapies directed at solid tumors. A drug that selectively kills cells that are highly expressing CD206 is expected to have an overwhelming, immediate, conspicuous, and easily measured effect on KS tumors," said Frederick Cope, PhD, MS, FACN, CNS, senior vice president and chief scientific officer of Navidea. "This grant will bring us to submission of an IND and the first time human evaluation for a Manocept immunotherapeutic. We anticipate if trials are successful, we can bring an effective and life-sparing new therapy to KS patients who are in desperate need for such a new treatment."

"The Manocept platform may offer a unique approach to the treatment of Kaposi's sarcoma (KS) and is, we believe, a translational portal to the therapy of a number of other solid tumors in which macrophages and tumor-associated macrophages play a key role in tumorigenesis and metastasis," said Michael Goldberg, MD, chairman of the board of Navidea, "We believe that KS serves as model for a development strategy that can be expanded to other macrophage-dependent solid tumors as well as a model for therapeutics targeting viruses that incubate in macrophages. We are encouraged that our therapeutic program has been recognized by the NIH so soon after we began our therapeutic development effort. We plan on submitting additional grant requests as soon as we obtain results from the multiple ongoing studies in various cancer models, which should read out shortly."

These IND-enabling studies will be conducted in three parts. Part 1 studies require *in vitro* and cell culture experiments related to safety and efficacy of an intravenous injection of MT100. In part 2 and 3, nine preclinical animal studies will build on the part 1 results

and will further refine safety and efficacy variables including dosing and drug administration regimens and evaluating the feasibility of the MT 1000-class of molecules, as a novel treatment for KS. Following these studies, Navidea expects to submit an IND application to the FDA seeking permission to begin phase 1/2 clinical evaluation of MT1001 in KS patients.

Kaposi sarcoma (KS) is a serious and potentially life threatening illness in persons infected with HIV, the causative agent of acquired immunodeficiency syndrome (AIDS). Tumor associated macrophages (TAMs) constitute an important tumor component for most types of cancer (including KS) that contributes to tumor growth and protection from immune responses. Navidea, through its subsidiary Macrophage Therapeutics, is developing a receptor targeted drug construct that may be able to effectively treat KS and could contribute to effective immunotherapy for a wide variety of cancers.

Navidea Biopharmaceuticals is developing Manocept, a new pharmaceutical platform technology, targeting cells that express the macrophage mannose receptor (CD206). A wide variety of immune-targeting applications for this platform technology are envisioned. Macrophages play important roles in many disease states and are an emerging target in many disorders. This flexible and versatile platform acts as an engine for purpose-built molecules that may enhance diagnostic accuracy, clinical decision-making, targeted treatments, and ultimately patient care. As an immunodiagnostic tool, the Manocept technology can utilize a breadth of imaging modalities, including SPECT, PET, intraoperative, and/or optical-fluorescence detection. By linking a therapeutic agent on the Manocept molecular backbone, there is the potential to develop novel, targeted immunotherapies specifically designed to selectively deliver an agent that can kill or alter disease-associated macrophages. MT1000 class of compounds, consisting of a Manocept construct linked to doxorubicin, is the first in a series of drug delivery constructs that will utilize Navidea's Manocept CD206 targeted drug delivery platform. Navidea's FDA-approved immunodiagnostic agent, Lymphoseek® (technetium 99m tilmanocept) injection, is representative of the platform's ability to successfully exploit this mechanism and offer the potential for development of new CD206-targeted immunodiagnostic agents and immunotherapeutics. The development activities of the Manocept immunotherapeutic platform will be conducted by Navidea's subsidiary, Macrophage Therapeutics.

Lymphoseek® (technetium Tc 99m tilmanocept) injection is the first and only FDA-approved receptor-targeted lymphatic mapping agent. It is a novel, receptor-targeted, small-molecule radiopharmaceutical used in the evaluation of lymphatic basins that may have cancer involvement in patients. Lymphoseek is designed for the precise identification of lymph nodes that drain from a primary tumor, which have the highest probability of harboring cancer. Lymphoseek is approved by the U.S. Food and Drug Administration (FDA) for use in solid tumor cancers where lymphatic mapping is a component of surgical management and for guiding sentinel lymph node biopsy in patients with clinically node negative breast cancer, melanoma, or squamous cell carcinoma of the oral cavity. Lymphoseek has also received European approval in imaging and intraoperative detection of sentinel lymph nodes in patients with melanoma, breast cancer, or localized squamous cell carcinoma of the oral cavity.

Accurate diagnostic evaluation of cancer is critical, as results guide therapy decisions and determine patient prognosis and risk of recurrence. Overall in the United States, solid tumor cancers may represent up to 1.2 million cases per year. The sentinel node label in the United States and Europe may address approximately 600,000 new cases of breast cancer, 160,000 new cases of melanoma, and 100,000 new cases of head and neck/oral cancer diagnosed annually.

Navidea Biopharmaceuticals, Inc. (NYSE MKT: NAVB) is a biopharmaceutical company focused on the development and commercialization of precision immunodiagnostic agents and immunotherapeutics. Navidea is developing multiple precision-targeted products and platforms including Manocept™ and NAV4694 to help identify the sites and pathways of undetected disease and enable better diagnostic accuracy, clinical decision-making, targeted treatment, and ultimately, patient care. Lymphoseek® (technetium Tc 99m tilmanocept) injection, Navidea's first commercial product from the Manocept platform, was approved by the FDA in March 2013 and in Europe in November 2014. The development activities of the Manocept immunotherapeutic platform will be conducted by Navidea in conjunction with its subsidiary, Macrophage Therapeutics. Navidea's strategy is to deliver superior growth and shareholder return by bringing to market novel products and advancing the company's pipeline through global partnering and commercialization efforts. For more information, please visit [www.navidea.com](http://www.navidea.com).

Macrophage Therapeutics, Inc., a subsidiary of Navidea Biopharmaceuticals, Inc. (NAVB), is developing therapeutics using the patented Manocept immunotherapy platform licensed from Navidea to target overactive macrophages implicated in cancer, cardiovascular, central nervous system, autoimmune, antiviral, and skin diseases. Manocept specifically targets CD206, or the mannose receptor prevalent on overactive macrophages. The technology enables highly specific targeted delivery of active (either existing or yet to be developed) agents that can modulate the activity of overactive macrophages that have been implicated in many diseases. Targeted delivery should significantly enhance a given compound's efficacy and safety.

## **Nanologica and Alcyone Lifesciences to Collaborate via Licensing Agreement**

Business Wire: May 16, 2016 – STOCKHOLM, Sweden – Nanologica entered into a license and collaboration agreement with Alcyone Lifesciences to develop Abela, a treatment for motor neuron disorders including ALS.

Nanologica today announced that it has entered into a License and Collaboration Agreement with Alcyone Lifesciences to develop a novel therapeutic platform named Abela; “to breathe” in Hebrew. The partners want to combine Nanologica’s NLAB Silica™ with Alcyone’s proprietary drug delivery platform technology. The goal is to develop and commercialize through partnership with biopharma a treatment of certain motor neuron disorders, including amyotrophic lateral sclerosis (ALS), based on targeted and sustained delivery of trophic factors in combination with embryonic stem cell derived cells. The role of trophic factors is to rescue degenerating neurons or to support survival of transplanted stem cells in patients with ALS or other motor neuron disorders.

“We are excited to kick off the Abela program with Alcyone Lifesciences. The collaboration offers a novel approach to treat ALS patients. We’re very satisfied with the match, not only scientifically but also culturally. The Alcyone team has, in a very inspiring way, repeatedly demonstrated an ability to think outside the box when it comes to therapeutic delivery, which is needed when taking on such a challenge as ALS,” said Nanologica CEO Andreas Bhagwani.

According to the license and collaboration agreement, Alcyone will operate the Abela program and will be responsible for further development and financing of the program through collaboration with biopharma.

ALS is a fatal neurodegenerative disease that affects nerve cells in the brain and spinal cord. It usually starts with loss of control of limbs or difficulties in swallowing related to muscle weakness. Most patients suffer a rapid decline in motor function and die within 2–5 years due to inability to breathe in most cases. There is currently no cure for ALS. Only one drug has been approved for the treatment of ALS, with a limited clinical benefit of slowing down the progression of disease. There are currently more than 70,000 ALS patients in the United States and Europe alone who would benefit from a new therapy.

“It is the science that excites us. Alcyone’s objective is to help to solve some of the most important and challenging problems in CNS medicine. We believe the key to potential success of this therapy is a delivery system like Alcyone’s platform technology that delivers in a targeted manner the trophic factors encapsulated in Nanologica’s nanoporous material and that provides a specific level of active molecules exactly where they are needed over a prolonged time. That is where we believe a combined approach can potentially make a difference clinically. The Alcyone team is delighted to work with Andreas Bhagwani, Adam Feiler, and the rest of the talented Nanologica team, as well as Prof. Elena N. Kozlova at Uppsala University” said P.J. Anand, founder and CEO of Alcyone Lifesciences.

In previous work, Nanologica in collaboration with Prof. Elena N. Kozlova (Uppsala University) demonstrated sustained delivery of trophic factors for survival and functional differentiation of stem cells by using nanoporous silica particles.

Abela is a joint effort between Nanologica and Alcyone Lifesciences to fulfill the vision of delivering trophic factors in combination with embryonic stem cell-derived cells in a precise and slow-release manner, to combat motor neuron loss leading to progression of motor neuron disorders including ALS.

Nanologica develops nanoporous silica for applications in life science. The company focuses on two business areas: drug delivery and chromatography, a technology used for the separation and purification of products on the market and in development. Nanologica’s core competency is to apply its unique know-how in the field of material science for developing nanoporous silica particles with unique characteristics. Based in Södertälje, Sweden, Nanologica has 19 employees from 10 nationalities, of which 10 are PhDs. For more information, please visit [www.nanologica.com](http://www.nanologica.com).

Alcyone Lifesciences, based in Lowell, Massachusetts, U.S.A., is a privately held neuroscience medical device company focused on development of novel treatment modalities for chronic neurological conditions. The company’s patented technology platform is based on a uniquely engineered amalgamation of microfabrication technologies along with advanced biomedical engineering with core product focus on targeted CNS therapy and hydrocephalus. Alcyone’s team of scientists, physicians, and advisers includes recognized leaders in the field of neurology and neurosurgery. For more information, please visit [www.alcyonels.com](http://www.alcyonels.com).



### **NLS Pharma Announces Submission of Investigational New Drug (IND) Application to FDA for Its Controlled-Release Mazindol for the Treatment of Adults with Attention-Deficit/Hyperactivity Disorder (ADHD)**

Business Wire: May 12, 2016 – PARIS, France, and STANS, Switzerland – NLS Pharma Group announced the submission of an Investigational New Drug Application (IND) with the U.S. Food and Drug Administration (FDA) to initiate a phase IIb clinical trial with its lead compound Mazindol. The study is entitled “A Double-Blind Placebo-Controlled phase IIb Study to Determine the Efficacy, Safety, Tolerability and Pharmacokinetics of a Controlled Release (CR) Formulation of Mazindol in Adults with DSM-5 Attention Deficit Hyperactivity Disorder (ADHD).”

The principal investigator of the study will be Dr. Tim Wigal, who brings extensive experience in clinical research, diagnosis, and treatment of ADHD to the project. Dr. Wigal has been author or co-author of over 125 journal articles about ADHD and related disorders. Seven clinical sites in the United States will participate in the study.

ADHD is considered by OECD as one of the most frequently monitored developmental syndromes worldwide. In early adulthood, ADHD may be associated with depression, mood or conduct disorders, and substance abuse. Adults with ADHD often cope with difficulties at work and in their personal and family lives related to ADHD symptoms. ADHD is still far from being well addressed.

Currently, first line treatments for ADHD mainly rely on the use of psychostimulants such as methylphenidates and amphetamines, along with the non-amphetamine-like stimulant modafinil. Certain adverse events have often been observed when using these types of products, impacting patients' everyday life, suggesting that better options for all patients are needed.

“With the submission of this IND, NLS Pharma has achieved an additional major milestone in its development program of NLS1001 for ADHD,” stated Alex Zwyrer, chief executive officer of NLS Pharma.

NLS Pharma has been created to fulfill medical needs of patients with neurobehavioral and neurocognitive disorders, where there is unmet medical need. It is supported by a worldwide network of opinion leaders and academic institutions, relying on a team of experienced industry development experts and well-recognized pharmaceutical leaders.

Attention deficit hyperactivity disorder (ADHD) is a group of behavioral symptoms that include inattentiveness, hyperactivity, and impulsiveness.

The worldwide prevalence, for those under the age of 18, is estimated to be 5.3–12% (*American Journal of Psychiatry* 2007). In the United States, approximately 6.4 million people under the age of 18 have been diagnosed with ADHD at some point in their lives. It is estimated that well over 10 million adults in the United States have ADHD (*Journal of the American Academy of Child and Adolescent Psychiatry* 01/2014).

ADHD treatment market value is expected to rise with a compound annual growth rate (CAGR) of 5.3%. ADHD therapeutics market value will rise from \$6.9 billion in 2013 to \$9.9 billion by 2020 (GBI Research 08/2014).

NLS Pharma is a Swiss-based biotech group focusing on the repurposing of established and (cost-)effective drug/chemical compounds to treat attention deficit hyperactivity disorder (ADHD), sleep disorders, and cognitive impairment.

NLS develops innovative therapeutic solutions and prioritizes its work based on unmet medical needs, strong scientific understanding of neurobehavioral and neurocognitive disorders and their pharmacognosia.

NLS is a fully private owned enterprise managed by a top-level team of experts who have proven their value and experience with Big Pharmas. They work closely with renowned ADHD and sleep-related disorders opinion leaders.

Series-A financing was successfully completed for \$8.5 million on August 31, 2015, to secure proof of concept of the clinical development of mazindol in ADHD. For more information, please visit [www.nlspharma.com](http://www.nlspharma.com). ■