

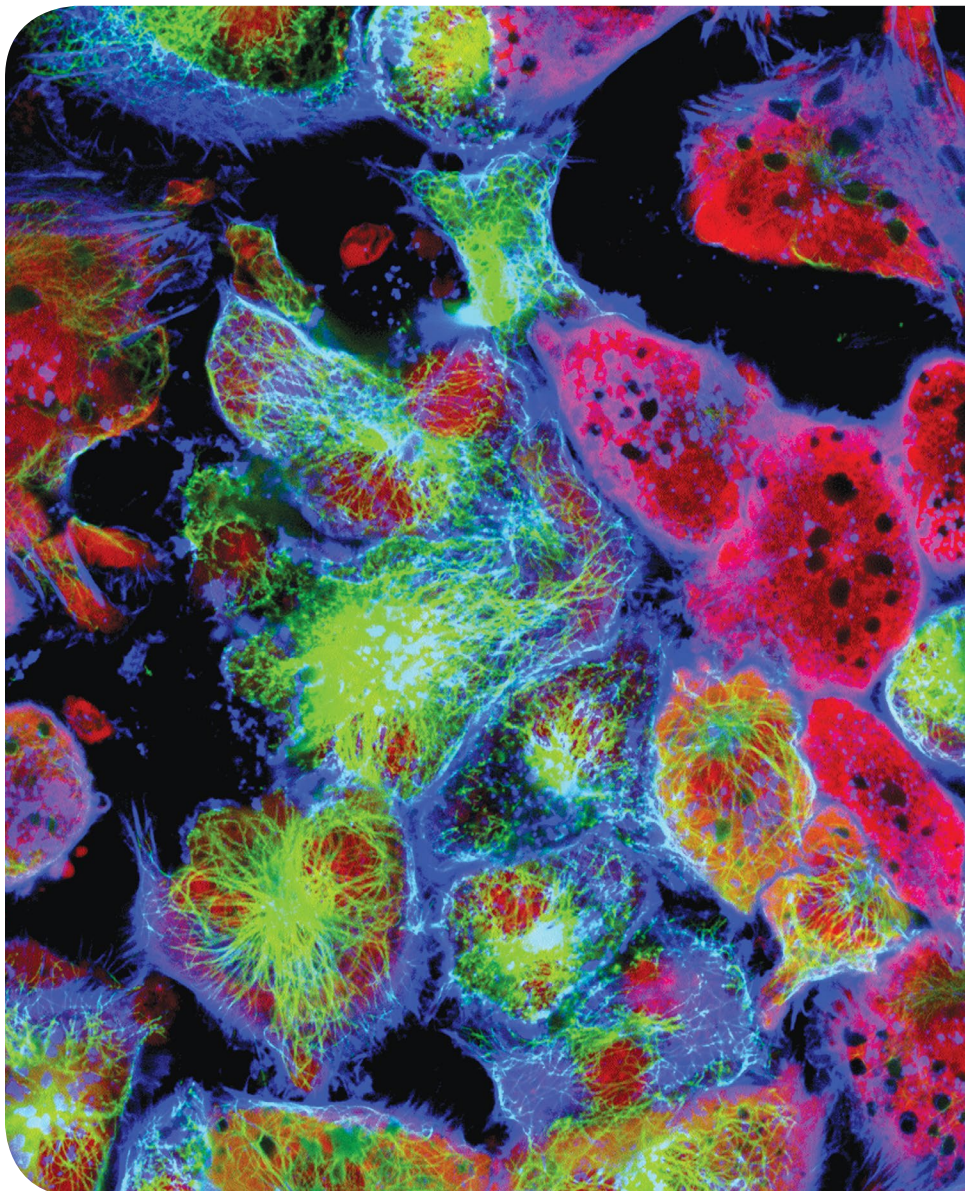
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Computational Modeling Using
the Multiscale Modeling Paradigm:
Liposome-Based Drug Delivery
Systems as a Case Study

Fluorescent Imaging of COX-2 in
Pathological Tissues by Fluorocoxib
A-Loaded Nanoparticles

Interview with Mauro Ferrari,
Academic Entrepreneur and
Pioneer in Nanotechnology

Patent Watch





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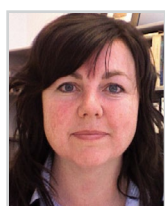




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Cover image: Tumor cells under microscope labeled with fluorescent molecules © Vshivkova / Shutterstock.com

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Distance Learning

We are well into the new academic year and—for those of us in the Northern hemisphere—packing up all our memories from hopefully a wonderful summer.

Teaching is on my mind at this time, in particular an awareness of the increasing numbers of distance education programs and institutions offering nontraditional degrees. Much of this is due to the demands of modern life and also the financial benefits (not having to live on campus, etc.). I asked myself, how new is this educational approach?

Apparently, distance learning is not really that new at all. It was introduced in the United States in 1728 in Boston. Educational materials were sent out using the postal service to students around the country, and it was relatively popular in several subjects, particularly agriculture. Since many students resided in rural areas, this was an attractive way of providing them with educational opportunities. Once the radio was available, distance learning spread to the Arctic Circle.

Over “the pond,” in 1858 the University of London became the first institution to provide full distance learning degrees in literature and the fine arts. Then came the Open University, established in 1969. It started television broadcasts in January 1971 that stopped in 2006 in favor of DVDs, the internet, and written and audio materials. This has now become one of the biggest universities in the United Kingdom and Europe for undergraduate education, with over 250,000 students enrolled (including more than 50,000 overseas). The Open University also offers graduate education, with research in over 25 areas and 1,200 participating students, and spends over £20 million on research. Reading over extensive information on their website and on Wikipedia, one wonders how the alumni have succeeded in their careers compared with those who have completed their education at a more traditional institution.

Acceptance of nontraditional, less expensive education is increasing, especially in these times of high tuition rates. There are so many potential student candidates for this e-learning approach, including mature working students who prefer not to drive to a campus through traffic after a hectic day at work, those with small children, those wishing for additional certifications after completing traditional degrees, and so on. With so many traditional universities currently expanding their distance learning options and the global client demand for e-learning, how will the high-tuition established institutions fare? How will they change? Will the students of tomorrow no longer have a move-in day on campus, dorm parties, and fraternity and sorority get-togethers? Will the professors no longer see the rows of faces in the class auditoriums? Will we miss this or not? The predictions are that with the issue of finances future students (and parents) will look more at e-learning as an option, and that means drastic changes to the lives of teachers and the institutions we know today. This will in turn change how and whom the industry recruits and how the workforce will be trained.

We have a great issue again (that in part provides us all with some distance learning) with stimulating articles and a scientific interview with Mauro Ferrari from the Methodist Hospital Research Institute in Houston.

Wishing you happy reading and a productive year. ■

Academic Entrepreneur and Founder in the Field of Nanotechnology: Mauro Ferrari of the Methodist Hospital Research Institute, Houston, Texas

Vishwas Rai¹ and Bozena B. Michniak-Kohn²

Mauro Ferrari is the executive vice president of Houston Methodist Hospital (a *U.S. News and World Report* Honor Roll Hospital, 2016) and the president/CEO of the Houston Methodist Research Institute, where he is the Ernest Cockrell Jr. Presidential Distinguished Chair. He also serves as the senior associate dean of the Weill Cornell Medical College, the primary academic affiliate of Houston Methodist. He has served as a special expert and advisor to the director of the National Cancer Institute (2003–2005), leading the establishment of the Alliance for Nanotechnology in Cancer, the world's largest program in nanomedicine to date.

Dr. Ferrari is a member of the National Academy of Sciences of Italy and the European Academy of Sciences and is a fellow of the American Academy for the Advancement of Science, the American Institute for Medical and Biological Engineering, and the American Society of Mechanical Engineers.

His current duties include executive responsibilities over all research and education programs at Houston Methodist, with over 1,200 research employees and accredited clinicians executing more than 1,000 clinical trials and protocols. During his academic journey, his research work primarily focused on drug delivery, cell transplantation, implantable bioreactors, and other innovative therapeutic modalities. He has contributed several firsts in the course of his career, including the first nanofluidic systems (1992), microchip-cell hybrid therapeutic implants (1995), silicon-based therapeutic particles (1998), nanostructured surfaces for proteomics and peptidomics (2005), multi-stage vectors for systemic therapy (2008), formulation of transport oncophysics (2011), and injectable nanoparticle generators (2016) for the therapy of lung and liver metastases of mammary carcinomas.



Mauro Ferrari in front of the Houston Methodist Research Institute he inaugurated in 2011.



With his wife, Paola, after completing his sixth Houston Marathon, with his personal record, in 2016.

Dr. Ferrari earned his degree of Dottore in mathematics at the University of Padova, Italy (1985) and then completed M.S. (1987) and Ph.D. (1989) degrees in mechanical engineering at the University of California, Berkeley, while also serving (1988–1990) at the University of Udine in Italy as an assistant professor of theoretical and applied mechanics. He was appointed to the faculty of the University of California at Berkeley, where he served as an assistant and then tenured associate professor of materials science, civil engineering, and bioengineering (1991–1998). From 1999 to 2006, he served at Ohio State University as the Edgar Hendrickson Professor and Director of Biomedical Engineering and a professor of internal medicine, mechanical engineering, and materials science, as well as the associate vice president for health science technology and commercialization. While at Ohio State he also attended medical school (2002–2003). Before joining Houston Methodist Research Institute in 2010, he served as a tenured professor of nanotechnology and internal medicine at the University of Texas Health Science Center for four years (2006–2010), where he was the founding chairman of the first department of nanomedicine in any medical school. During his academic and industrial career, he has published more than 350 papers and seven books.

He is the inventor of more than 40 issued patents, with about 30 more pending in the United States and internationally. His personal career research and development portfolio as a principal investigator totals over \$100 million, including support from the National Cancer Institute (NCI), National Institutes of Health, NASA, National Science Foundation, Defense Advanced Research Projects Agency, U.S. Department of Energy, the FDA, the state of Texas, the state of Ohio, and several private enterprises.

continued

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He was the recipient of the prestigious CRS Founder's Award at the 38th Annual Meeting & Exposition in 2011. His contributions have received a variety of other accolades, including the Wallace H. Coulter Award for Biomedical Innovation and Entrepreneurship, the ETH Zürich Stodola Medal, the Blaise Pascal Medal in Biomedical Engineering from the European Academy of Sciences, and the Innovator Award from the Breast Cancer Research Program of the Department of Defense. He received the Robert Heinlein award for microgravity research, and his experiments have flown on the International Space Station. He holds honorary doctorates in electrical engineering and biotechnology from the University of Palermo and the University of Naples "Federico II," respectively, and adjunct or visiting faculty positions at many prestigious academic institutions worldwide.

Q *With an academic background spanning mathematics to mechanical engineering, what inspired you to join the field of biomedical nano- and microtechnology and make a significant impact in the field?*

A Well, back in those days there wasn't a "field" yet, just a few people here and there that were starting to see the opportunity for breakthroughs based on interdisciplinary perspectives. The word BioMEMS originated in my lab at Berkeley in the early 1990s, and the words nanotechnology and cancer had not been used in the same sentence just yet. I guess that's another way to say how old I am getting! But, seriously now, the reason why I got started in this direction was that my wife, Marialuisa, got sick with cancer and died. I knew nothing about medicine, so the only thing I could bring to the fight against cancer was what I knew something about: microtechnology, which over time became nanotech, and some mathematical physics.

Q *Do you still maintain an active research lab? What are some of the important projects you are involved in?*

A Yes, I maintain a very active lab. I just could not be without a lab. I have passed on to some of my younger collaborators some of my research lines—and they are doing better with them than I ever could have! The nanofluidics work is now directed by Alessandro Grattoni, who has actually gotten it on the International Space Station, among other things. The bone regeneration platform, BioNanoScaffold, is worked on by an interdisciplinary team taking it to the clinic under the guidance of our chief spinal surgeon, Brad Weiner. Tony Hu is taking the proteomic nanotechnology in new, fully independent directions. There are about 100 people at Houston Methodist alone working on different variants of our multistage vector therapeutics. I remain mostly involved in novel designs, such as our new injectable nanoparticle generator drugs (iNPG-pDox), in close collaboration with Haifa Shen, Elvin Blanco, and Joy Wolfram. We recently published back-to-back papers in *Nature Biotechnology*. The last one showed for the first time in history that it is possible to completely cure lung and liver metastases in animal models—this we are taking to the clinic with a great sense of mission, since it could dramatically change the way we deal with cancer. We were recently awarded a multi-investigator U54 center by the NCI, to study how transport oncophysics and nanotechnology can lead to improvements in cancer immunotherapy. This is my third NCI center grant as a principal investigator, and seventh overall; I believe this shows our commitment to multidisciplinary teamwork.

Q *What is the current and future focus of research and development at the Houston Methodist Research Institute?*

A We focus on the clinical translation of transformational discoveries like the new drug for cancer metastases, or innovative ways to rehabilitate stroke patients even a long time after their injury, as well as methods to fully restore cardiac functions following ischemic damage. We have many teams on these and other cutting-edge problems in medicine, with a supra-disciplinary approach. We are a hospital, so we always put patients first, and that is why we are so focused on clinical translation. We build GMP facilities and perform GLP safety tests for the most promising of our discoveries. We even have an internal development fund that we use to support our most advanced programs, so that they can make it across the valleys of death of translation and into the clinic in the most efficient manner, safely, and as rapidly as possible.

Q *Please tell us in brief about companies that you either founded or were involved with during their inception. Please give any words of wisdom for aspiring entrepreneurs.*

A Entrepreneurship is essential for the process of translation of true innovation. I have started several companies; currently, I am on the board of Arrowhead Pharmaceuticals (NASDAQ: ARWR), which has among other products a potentially curative, nano-based, RNAi therapeutic against hepatitis B in phase II trials. I am also on the board of NanoMedical Systems. Academic entrepreneurship has become almost "mission impossible," so my recommendations to academic investigators are these: Don't try to be CEO. Don't take money from folks that are unable to lead in the next round. Don't start your company too soon (you will spend the rest of your life in zombified mode, or worse, if you do). Fully identify and derisk your product first! And make sure your lab is an institution that helps you do all of the above. Did I mention that we are always open for business, when it comes to recruiting extraordinary innovators?

Q Please elaborate on the current state of BioMEMS technology. What are some of the commercial successes with the technology?

A Frankly, diagnostic BioMEMS have not lived up to expectations, not because of the lack of technology excellence, but rather because of the financial dynamics of healthcare, where there is limited if any premium for screening and early detection, which is where BioMEMS offer the greatest advantages. And now we have to deal with the Theranos scandal, which will cast a negative light upon microfluidics and BioMEMS, in the impressionable eyes of the uninformed, although it has nothing to do with these fields and the underlying technology platforms developed by serious scientists that have given decades of their lives to these endeavors, with extraordinary successes. While Theranos, on the other hand...

Q Could you please highlight a few research articles from your work that you believe have made the most impact in the field?

A I will pick just articles that have gotten cover honors in *Nature* journals, from the many that we published there over the years.

This is the first article in a major journal anywhere that ties together nanotechnology and cancer:

Ferrari, M. Cancer nanotechnology: Opportunities and challenges. *Nat. Rev. Cancer* 5: 161-171 (2005).

The following two articles demonstrate the first multi-stage delivery systems for systemic injection and highlight the importance of physics and geometry in the rational design of nanoparticles:

Tasciotti, E, Liu, X, Bhavane, R, Plant, K, Leonard, AD, Price, BK, Cheng, MM, Decuzzi, P, Tour, JM, Robertson, F, Ferrari, M. Mesoporous silicon particles as a multistage delivery system for imaging and therapeutic applications. *Nat. Nanotechnol.* 3: 151-157 (2008).

Ferrari M. Nanogeometry: Beyond drug delivery. *Nat. Nanotechnol.* 3: 131-132 (2008).

By studying the transport properties of nanosystems inside cancers, we made a more general discovery: mass transport in cancer is truly different from its counterpart in healthy tissues, for all types of mass, including biological molecules, cells, conventional drugs, and so on. Based on this, I formulated the framework of transport oncophysics: cancer really is a proliferative disease of mass transport dysregulation, which occurs primarily because of pathologic evolution of the biological barriers inside the body. This opens up a whole world of opportunities for novel drug delivery systems!

Michor, F, Liphardt, J, Ferrari, M, Widom, J. What does physics have to do with cancer? *Nat. Rev. Cancer* 11: 657-670 (2011).

This last article could be the most important result I have ever worked with, for it provides the unprecedented opportunity to cure lung and liver metastases. These are the most prevalent cause of death in cancer.

Xu, R, Zhang, G, Deng, X, Mai, J, Segura-Ibarra, V, Wu, S, Shen, J, Liu, H, Hu, Z, Chen, L, Huang, Y, Koay, EK, Huang, Y, Liu, J, Ensor, JE, Blanco, E, Liu, X, Ferrari, M, Shen, H. An injectable nanoparticle generator enhances delivery of cancer therapeutics. *Nat. Biotech.* 34: 414-418 (2016).

Q Could you please highlight a few publications from other prominent researchers that you believe have made the most impact in the field of nanotechnology?

A Sure, with pleasure! In strict alphabetical order...

Mark E. Davis at Caltech developed CALAA-01, the first RNA-carrying nanoparticle to be evaluated in a clinical trial for solid cancers. This human trial involved systemic delivery of siRNA with a targeted delivery system to treat patients with metastatic melanoma.

Davis, ME, Zuckerman, JE, Choi, CHJ, Seligson, D, Tolcher, A, Alabi, CA, Yen, Y, Heidel, JD, Ribas, A. Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. *Nature* 464: 1067-1070 (2010).

Robert Langer is the maestro of biomaterials and drug delivery—and many other fields! Among his zillion exceptional contributions, here is perhaps the one I remember most fondly, since it struck me between the eyebrows like a bolt of lightning and really got my inspiration going in a way that shaped much of my work to follow.

Langer, R, Vacanti, J. Tissue engineering. *Science* 260(5110): 920-926 (1993).

Chad A. Mirkin is known for many inventions, including his development of nanoparticle-based biodiagnostics. Dip-pen nanolithography—which can be used to transfer molecules and materials to surfaces with sub-50 nm resolution to study nanoelectronics, surface assembly, cell-surface interactions, and catalysis—has been recognized in a 2012 special issue of *National Geographic* as one of the top 100 scientific discoveries that changed the world.

Piner, RD, Zhu, J, Xu, F, Hong, S, Mirkin, CA. Dip-pen nanolithography. *Science* 283(5402): 661-663 (1999).

Nicholas A. Peppas published numerous seminal papers. In particular, his publication entitled “Mechanisms of Solute Release from Porous Hydrophilic Polymers” helped set the groundwork for research in the development of microparticle delivery systems. Dr. Peppas also published the influential article “Opsonization, Biodistribution, and Pharmacokinetics of Polymeric Nanoparticles,” which contributed to the U.S. FDA approval of the covalent attachment of poly(ethylene glycol) (PEG) to drugs to improve their pharmacokinetic properties.

Korsmeyer, RW, Gurny, R, Doelker, E, Buri, P, Peppas, NA. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.* 15: 25-35 (1983).

Owens, DE, Peppas, NA. Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. *Int. J. Pharm.* 307: 93-102 (2006).

George M. Whitesides has pioneered so many important areas, but I will just cite two of my favorites. His highly impactful manuscript “Molecular Self-Assembly and Nanochemistry: A Chemical Strategy for the Synthesis of Nanostructures” led to the development of low-cost diagnostics and tools for global health. In “Self-Assembly at All Scales” he introduced the notion of nested information systems and the communication within them—a crucial concept for nanotechnology and nanomedicine.

Whitesides, GM, Mathias, JP, Seto, CT. Molecular self-assembly and nanochemistry: A chemical strategy for the synthesis of nanostructures. *Science* 254(5036): 1312-1319 (1991).

Whitesides, GM, Grzybowski, B. Self-assembly at all scales. *Science* 295(5564): 2418-2421 (2002).

Q Please tell us about some of the successful ventures that came out of nanotechnology research in the last two decades.

A Far and away the crown goes to the company that introduced Abraxane (paclitaxel-vectoring albumin nanoparticles) to cancer clinics, Abraxis BioScience, which has since been acquired by Celgene. It was the first-ever blockbuster drug to emerge from the nano-world; most importantly, it was the first drug even to be approved by the FDA with a mechanism of action based on the transport properties! This really ushers in a brave new world.

Q Where do you see the science of nanotechnology heading from its current state in the future?

A I am not interested in nanotechnology *per se*; my interest is in serving patients. Thus, I hope that nanotechnology will disappear, in the sense that it will become so successfully pervasive in the clinic that there will be no need for special identifiers. Just the natural thing, merged into other natural components of new solutions for the age-old problems of cancer: early detection, screening, prevention, therapy of metastases, enhancement of quality of lives—and better access for all, through a massive reduction of prices for cancer diagnostics and treatment!

Q Please tell us about your hobbies. What are your favorite activities in free time?

A My life is fully dedicated to family, work, and community service. I don't do “free time”—it is all woven into the same texture of life. I travel with my wife, Paola, and our five (grown-up!) kids. I volunteer at the hospital, sometimes play saxophone and write, but without any real successes to report...I like to run marathons and ultramarathons, and they are certainly more restful than a typical day at the office! ■



With his dog Camillo, volunteering at the ALS clinic at Houston Methodist Hospital.

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Helen Burt



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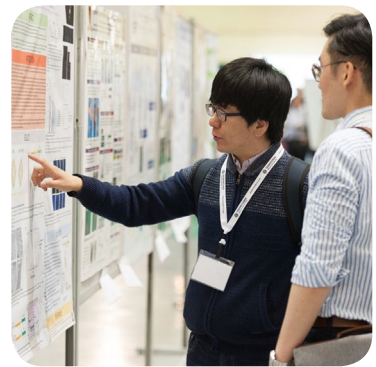
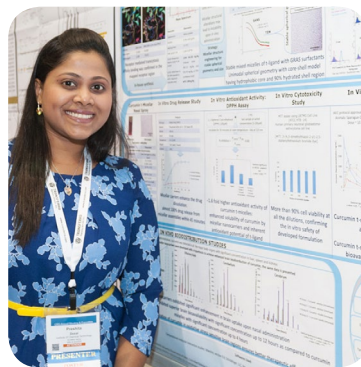
plenary speakers engaged attendees with their insight



Susan Hershenson

1

Founders Award Lecture:
2016 Awardee
Hans E. Junginger gave the
Founders Award Lecture



572

scientific posters explained breakthrough research in delivery science



9

industry-sponsored roundtables inspired thought-provoking discussion

66 exhibitors introduced cutting-edge technology, products, and services



56 invited speakers encouraged discussion through presentations and dialogue



12

students were awarded the Allan Hoffman Student Travel Grant to attend the 2016 annual meeting



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This year's theme "Collaborate, Connect, Innovate" brought together a dynamic meeting of the minds in Seattle, Washington, with over 65 exhibitors. These organizations support the research and development needs of delivery science and technology with innovative products and services, and they helped make the annual meeting a terrific success. Thank you 2016 CRS exhibitors!

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Computational Modeling Using the Multiscale Modeling Paradigm: The Key to Achieving Rational Design in Nanomedicine; Liposome-Based Drug Delivery Systems as a Case Study

Alex Bunker, Centre for Drug Research, Division of Pharmaceutical Biosciences, Faculty of Pharmacy, University of Helsinki, Finland

This first wave of computational modeling in pharmaceutical science was the application of informatics-based methods to finding optimum drug molecule structures: drug design. We can now move beyond this, both from drug design to the design of drug delivery vehicles, nanomedicine, and from raw optimization to a tool capable of obtaining insight that will, in combination with complementary experimental methodologies, allow for such vehicles to be created through a rational design process akin to engineering machines. Our work on applying computational modeling to determine aspects of the structure and behavior in the bloodstream of liposome-based drug delivery systems (LDS) represents a case study in how this can be achieved.

Through nanomedicine, the development of nanoscale drug carriers known as nanoparticles (NPs), lies the promise of delivery of drugs with vastly decreased toxicity and increased efficacy.¹ While there are several different forms of NPs, including polymeric micelles, solid NPs, dendrimers, and LDS, they all possess a common set of functional elements: 1) a core compartment where the drug to be delivered is stored, 2) a surrounding material that encapsulates the drug, 3) a protective sheath on the NP exterior that inhibits uptake by the mononuclear phagocyte system (MPS), and 4) possibly targeting moieties on the NP exterior to achieve active targeting. We are left with a wide array of metaphorical dials and switches to design NPs for optimized function. This includes the overall size of the NP and the formulation (molecules of which it is composed) of each functional element.

While the number of input parameters at our disposal in NP design is considerable, linking them to the structure and function of the NP is, however, not trivial; several factors beyond our control determine this, and our ability to elucidate the structure and function of NPs through experimental means alone thus remains limited: for the most part, NP design has been carried out through mostly trial and error based methodologies. We would argue that this is an important factor in why this field has, so far, been much more successful at generating publications than new drug therapies.² Many experimental methodologies exist to study aspects of NP structure and function, each capable of monitoring a different separate aspect of the system; however, the collective insight is still incomplete. The situation is comparable to the parable of the blind men and the elephant: one grabs the trunk and thinks they touch a snake, another the tail and believes it to be a rope, another the leg and believes it a tree, and so on. Computational modeling using the multiscale modeling paradigm³ is just the tool capable of filling in the gaps and revealing the elephant.

When a NP is in the bloodstream its structure and behavior are manifested over a broad range of length and time scales. No single technique can hope to model all of this at once. Instead, several different models with different assumptions are used in conjunction, each one suited to a different range of length and time scales. At the bottom, covering the smallest scale, is molecular dynamics (MD) modeling with all-atom resolution. The real interactions between the atoms and molecules, on a fundamental level governed by quantum mechanics, can be approximated through a classical model: molecules as assemblies of metaphorical solid balls connected by springs and hinges that in turn collide with one another, through nonbonded interactions between all atoms. The result is what has been described by Klaus Schulten and coworkers as a “computational microscope,”⁴ essentially a holographic movie of the system with all-atom resolution and length and time scales of around 10–20 nm and around 0.5–1 μ s, respectively. To reach larger length and time scales, this metaphorical microscope can be refocused through coarse graining: models with particles that are not single atoms but rather groups of atoms or even larger structures,³ for example, the MARTINI⁵ force field or the even more coarse-grained dissipative particle dynamics.³ Finally, at the top end are continuum models, with parameters determined by smaller-scale simulations, capable of reaching up to the macroscopic scale.

Our work, carried out over the past eight years, using molecular dynamics modeling with all-atom resolution to study LDS-based drug therapies, can be seen as a case study in how computational modeling can be used as a design tool in nanomedicine. In our work we have provided insight into four main areas: 1) the protective poly(ethylene glycol) (PEG) sheath (PEGylation), 2) targeting ligand design, 3) membrane formulation, and 4) interaction between the membrane and drugs carried by the LDS. Our work is described in detail in our recently published comprehensive review paper⁶ and two more recent publications.^{7,8} We will merely outline our work here and refer our readers to these three cited papers for a more complete understanding of what we have achieved.

continued

The first issue we approached was the behavior of the PEG polymer coating of the LDS: PEGylation. The motivation for this research is that, although PEG is effective as a protective polymer corona, there is significant room for improvement, and the search for alternatives is an active field of research. We started from the simplest models of a gel and liquid crystalline membrane with and without PEGylation and then added in levels of complexity one by one: varying PEG concentration and inserting cholesterol into the membrane to duplicate the formulation of Doxil[®],⁹ the first approved PEGylated liposome-based therapy (Figure 1). We looked at the behavior in plasma though inclusion of NaCl at a level of 125 mM and also investigated KCl and CaCl₂ at the same ionic strength.

We found behavior that should have been expected, given what was previously known about PEG as a polymer on its own, but that in the context of use in LDS-based therapies was unanticipated. Because PEG is a polymer electrolyte it associates strongly with the Na⁺ ions. Also, PEG is known to be soluble in a wide range of both polar and nonpolar solvents and as a result entered into the membrane core of the more loosely structured liquid crystalline membrane but did not for the case of the gel membrane. When we simulated the Doxil[®] formulation⁹ with cholesterol in the membrane, the PEG entered into the membrane but in a specific fashion: winding along the β surface of the cholesterol molecules, thus disrupting the role they normally play in condensing the membrane. The density of the PEG layer was found to have an important effect: at 5% formulation density of PEGylated lipids the Cl⁻ ions, with their tightly bound water shells, were found to sit in water pockets in the PEG layer. When the formulation density of PEGylated lipids was raised to 10% the Cl⁻ ions and their tightly bound water shells were expelled from the PEG layer. Thus, as the formulation density of PEGylated lipids increases, the effective surface charge of the liposome, positive in the absence of a PEG corona due to Na⁺ ions bound to the lipid headgroups, initially decreases; however, when the formulation density of PEGylated lipids is increased beyond a certain density, the surface charge starts increasing again. Because surface charge plays an important role in MPS uptake, this could explain the previously observed optimum PEGylated lipid density. It was also found that the divalent Ca²⁺ ions did not bind to PEG at all, preferring to bind to the lipid headgroups. It has previously been observed that PEGylation inhibits calcium-induced liposome fusion via headgroup crosslinking, and now this provides a mechanism: steric hindrance.

Active targeting design currently involves a significant degree of trial and error; ligands that yield positive results in isolated docking to their targets often fail *in vivo* when attached to the surface of the liposome. We have demonstrated that computational modeling has the capacity to yield significant insight here. In one example we studied a new targeting ligand, the activated endothelium targeting peptide (AETP) moiety, that was more hydrophobic than a similar ligand, the arginyl-glycyl-aspartic acid (RGD) peptide (Figure 2), which had previously been shown to work. Although the AETP moiety passed phage display screening it failed *in vivo*. Our computational modeling showed the cause of this failure: it was not, as previously suspected, that the ligand entered into the membrane core, but rather it was obscured by the PEG polymer itself. Thus, we could suggest that replacing the PEG polymer with a possibly more hydrophilic polymer could solve this problem. We also worked with an Indian research group developing LDS-based therapies to target liver cancer and showed with our simulations that exposure to the solvent was increased by polymerization of the ligand.⁷

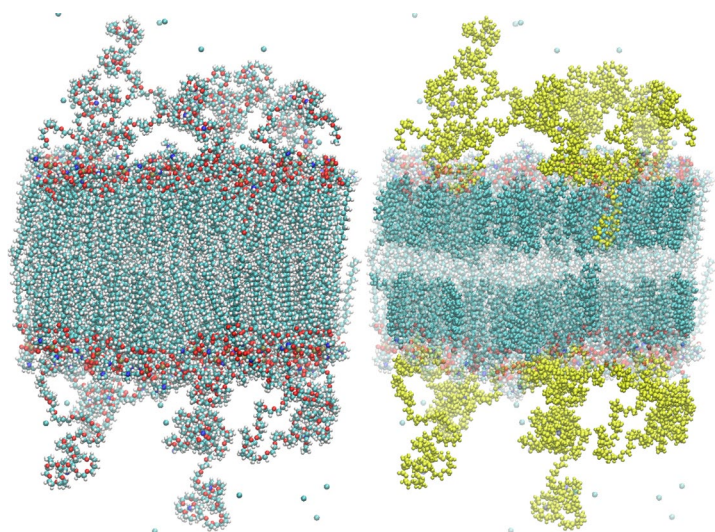


Figure 1. Model with all-atom resolution of the Doxil membrane; right panel highlights the 1,2-dioctadecanoyl-sn-glycero-3-phosphoethanolamine (DSPE)-PEG lipids in yellow and the cholesterol molecules in aquamarine.

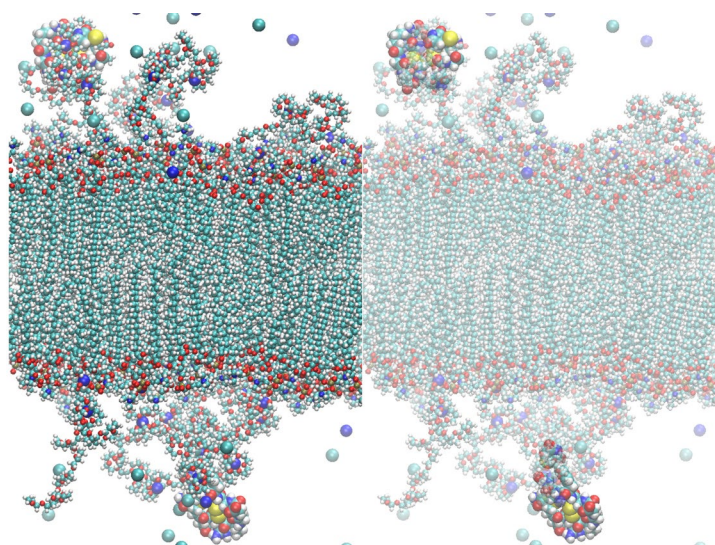


Figure 2. Doxil formulation with targeting ligand, in this case the RGD peptide; right panel highlights the ligand.

In other work we investigated the structure of lipid membranes composed of synthetic lipids, for example, the membrane of a liposome proposed by the Szoka group with the phosphate and choline groups switched. Although this seems like a trivial change, we determined that the result significantly altered membrane properties: the membrane no longer binds Na^+ ions, and the water ordering at the membrane surface is reversed, a feature that possibly aids drug delivery through the cell membrane. We have also studied the behavior of drugs being delivered by PEGylated liposomes, for example, indocyanine green (Figure 3), and found that hydrophobic drugs can sit either in the membrane or the PEG layer; however, where they locate is determined by their starting point in the simulation.⁸ This indicates the possibility that the location of drugs in the liposome can be controlled through formulation.

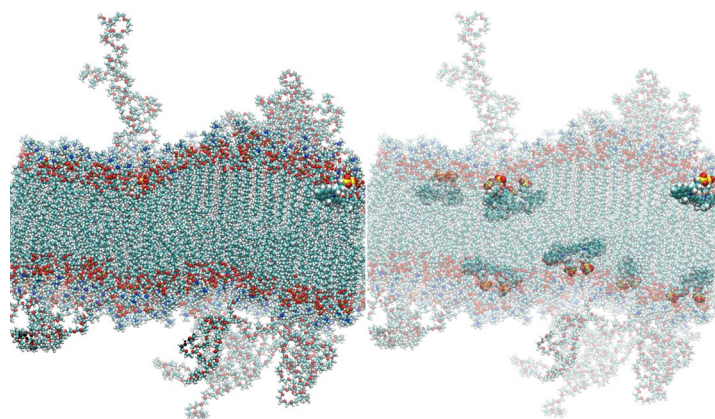


Figure 3. Indocyanine green in the PEGylated membrane; right panel highlights the indocyanine green molecules.

Our work in this area continues; we are currently working on improving the existing coarse-grained force fields to allow us to investigate larger-scale properties of LDS-based delivery systems and ultimately use the insight from these simulations to construct continuum models capable of studying the entire LDS in the bloodstream. Our intention is ultimately to present our methodology as a novel framework in which computational modeling is applied in concert with complementary experiments to build the next generation of NPs using a rational design approach: as nanoscale engineered machines, or, to use the colloquial term, *nanobots*.

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Fluorescent Imaging of COX-2 in Pathological Tissues by Fluorocoxib A-Loaded Nanoparticles

Md. Jashim Uddin,^{a,b} Thomas A. Werfel,^{b,c} Brenda C. Crews,^a Mukesh K. Gupta,^c Taylor E. Kavanaugh,^c Philip J. Kingsley,^a Kelli Boyd,^d Lawrence J. Marnett,^{a,c} and Craig L. Duvall^{b,e}

Introduction

Overexpression of cyclooxygenase-2 (COX-2) is a hallmark of inflammation and an early event in carcinogenesis and cancer progression.^{1,2} Because COX-2 is expressed in virtually all solid tumors, it represents an ideal biomarker with broad impact for the early clinical detection of inflammatory disease and cancers. To this end, we previously developed the first fluorescent COX-2-specific inhibitor, fluorocoxib A (FA), to detect COX-2 expression in animal models of inflammation and cancer, suggesting it may be a valuable clinical tool for the early detection of cancers of the skin, colon, esophagus, bladder, and oropharynx.³ However, attempts to translate FA to the clinic have been hampered by its lack of solubility in aqueous solutions appropriate for human administration. We recently developed a FA nanoparticle (FA-NP) that enables fully aqueous solubilization and environmentally targeted release for clinical translation of FA. The FA-NP vehicle is based on a reactive oxygen species (ROS) responsive, diblock copolymer synthesized via a combination of anionic and reversible addition-fragmentation chain-transfer (RAFT) polymerization and chosen due to the connected overexpression of COX-2 and ROS production. Our recent report demonstrates the effective intravenous administration of FA in this water-soluble nano-formulation and selective targeting of FA-NPs to tumors and inflamed tissue sites with upregulated COX-2 relative to normal tissues.⁴

Materials and Methods

The new diblock polymer, poly(propylene sulfide)₁₀₆-*b*-poly[oligo(ethylene glycol)₉ methyl ether acrylate]₁₇ (PPS₁₀₆-*b*-POEGA₁₇), was synthesized by a combination of anionic and RAFT polymerization (Figure 1).⁵ FA-NPs and 5-carboxy-X-rhodamine (5-ROX) NPs (nonbinding control) were prepared via the bulk solvent evaporation method, in which FA or 5-ROX were codissolved with PPS₁₀₆-*b*-POEGA₁₇ in chloroform, added dropwise to phosphate-buffered saline (PBS) that was being stirred, and allowed to evaporate overnight. Sprague Dawley rats were injected in the rear right footpad with carrageenan to induce edema followed by intravenous injection of FA-NPs 2 h post-carrageenan and fluorescent imaging on a Xenogen IVIS 200 instrument. Nude female mice were inoculated with 1 × 10⁶ human 1483 head and neck squamous cell carcinoma (HNSCC) cells in Matrigel. Once tumors reached 800–1,000 mm³, mice were injected intraperitoneally or intravenously with FA-NPs and imaged 4 h post-injection on a Xenogen IVIS 200 instrument. To test the specificity of COX-2 labeling by FA-NPs, cohorts of rats and tumor-bearing mice were pre-dosed by injection with the cyclooxygenase inhibitor indomethacin 1 h prior to dosing with FA-NPs.

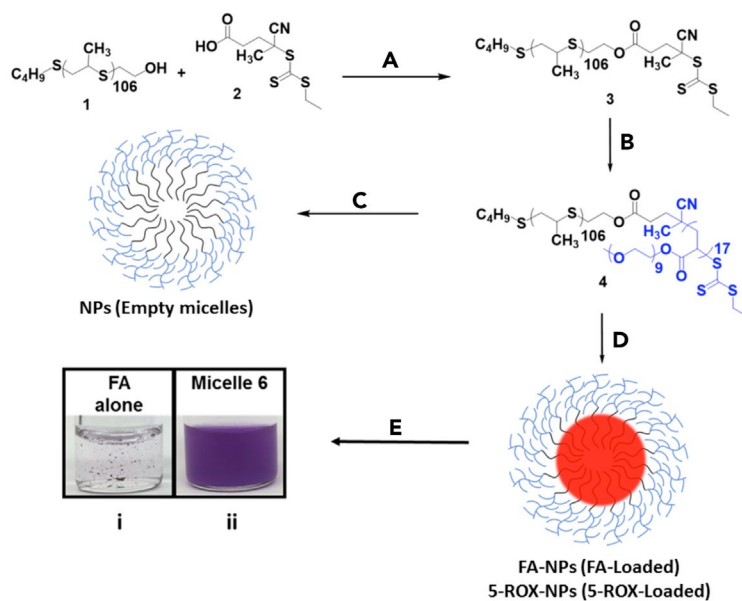


Figure 1. Synthesis of PPS₁₀₆-*b*-POEGA₁₇ and FA-PPS₁₀₆-*b*-POEGA₁₇. Conditions: (A) *N,N'*-dicyclohexylcarbodiimide, 4-dimethylaminopyridine, CH₃Cl, 25°C, 24 h; (B) POEGA, azobisisobutyronitrile, (CH₂)₄O₂, 70°C, 24 h; (C) CH₃Cl, PBS, 25°C, 24 h; (D) FA or 5-ROX, CH₃Cl, PBS, 25°C, 24 h; (E) solubilization of FA alone or FA-NPs in PBS, (i) FA (1 mg/mL) and (ii) FA-NPs (1 mg/mL FA).

continued

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Results and Discussion

A new nano-formulation of FA, FA encapsulated in water-soluble PPS₁₀₆-*b*-POEGA₁₇ micelles (FA-NPs), was recently characterized and validated in multiple pre-clinical animal models for detection of cancer and inflammation (Figure 2). This formulation overcomes the Achilles' heel of FA clinical translation, its lack of solubility in solvents appropriate for human administration. Initially, the physicochemical characteristics of FA-NPs (i.e., size, surface charge, drug loading, fluorescent properties, ROS degradability, and critical micelle concentration) were rigorously characterized and confirm that FA-NPs are a fully aqueous, intravenous-ready formulation of FA.

Analysis of the pharmacokinetics and biodistribution of FA-NPs revealed an optimal imaging window of 4–8 h post-injection, at which time FA is cleared from non-targeted major organs but persists within targeted tissue for high signal-to-noise ratio imaging. Using this optimal imaging window, we were able to distinguish 1483 HNSCC human tumor xenografts and carrageenan-induced inflammation of the rat foot pad from normal tissue *in vivo* (Figure 2A and D). Target tissue specificity in both models declined when the COX-2 active site was pre-blocked by the cyclooxygenase inhibitor indomethacin, confirming that FA-NPs release FA for molecular binding to COX-2 *in vivo* (Figure 2B and E).

Conclusions

Our collective data provide strong support for the utility of FA-NPs as a formulation strategy for detection of COX-2 in inflammatory tissues and premalignant or malignant tumors in clinical settings. Thus, FA-NPs overcome the major clinical limitation for FA, water insolubility, and represent the first feasible strategy for clinical translation of FA to detect pathological tissues containing elevated levels of COX-2.

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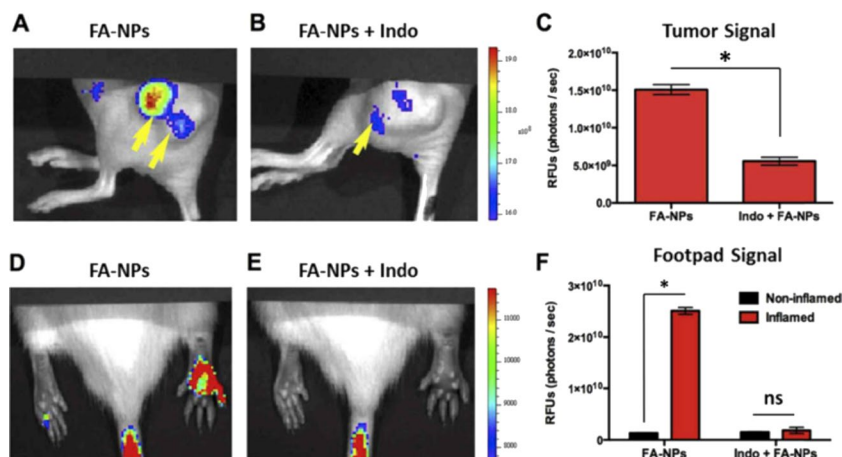


Figure 2. Targeted *in vivo* imaging of COX-2 in inflammation and cancer. (A–C) Female nude mice bearing COX-2-expressing 1483 HNSCC tumor xenografts were dosed with FA-NPs (1 mg/kg FA, intraperitoneal) and imaged at 4 h post-injection of NPs in a Xenogen IVIS 200 optical imaging instrument. A subset of animals was pretreated with indomethacin (Indo) to block the FA binding site on COX-2. (A–B) Fluorescence images of 1483 HNSCC tumor-bearing mice injected with FA-NPs with or without Indo pre-treatment 1 h prior to intraperitoneal injection of FA-NPs. (C) Quantification of images showing relative tumor signal ($n = 10$, $P = 0.003$). (D–E) Sprague Dawley rats with carrageenan-induced inflammation in their right hind footpads and with or without pre-injection of competitive COX-binding molecule Indo (2 mg/kg) were imaged 3 h post-injection with FA-NPs (1 mg/kg FA, intraperitoneal). (F) Quantification of signal in images of inflamed (carrageenan injected) versus non-inflamed footpads with and without Indo pre-treatment ($n = 8$, $P < 0.002$). RFU = relative fluorescence unit. © Elsevier; adapted with permission.⁴

Polymers that Deliver



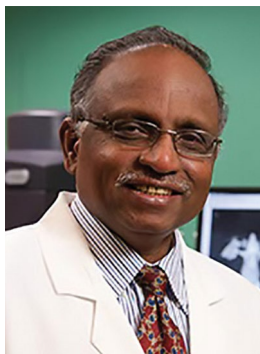
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Drug Delivery and Translational Research Update

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



Vinod Labhasetwar

At the *DDTR* editorial board meeting held during the CRS annual meeting in Seattle, I updated several parameters related to the journal and presented my vision for further growth. The most significant news was a 130% increase in citations compared with the year ending July 2015. Since the first impact factor (IF) for *DDTR* was announced in the summer of 2016, the journal is also receiving increased submissions. Along with *DDTR*, Thompson Reuters announced a list of 239 journals that received their first IF. I glanced through the list and randomly collected the IF of 24 journals that were the most relevant to medical, biological, and material sciences. The first IF of *DDTR* was 1.887, which was higher than the IF of around 80% of the journals from my list of 24. The journals with IF higher than *DDTR* were mostly clinical journals, which usually receive higher numbers of citations. Considering this analysis, I feel that *DDTR* did very well. *DDTR* is also developing several special issues that are focused on drug delivery in different disease conditions. The upcoming December issue is on ocular drug delivery. This elegantly developed special issue contains reviews and research articles that highlight advances in drug delivery for treating different eye conditions. You can access all *DDTR* articles for free as a member benefit by logging on to the CRS website.

Special Issue: Ocular Drug Delivery (Volume 6, Issue 6, 2016)

The estimated number of visually impaired people in the world is 285 million, with 39 million being blind and 246 million having low vision. About 65% of visually impaired people and 82% of all blind people are 50 years or older. Four major blinding diseases are age-related macular degeneration, diabetic retinopathy, diabetic macular edema, and glaucoma, and while there are many effective medications to treat these conditions, the challenge remains to deliver them effectively with a sustained release profile and with minimal side effects. One would think that a small organ such as the eye, which is readily accessible from the outside of the body, would be easy to treat. However, the eye is a rather isolated organ with a number of barriers in place to protect it from the environment, posing major challenges to effective drug delivery. Therefore, achieving sufficiently high concentrations at the target site and maintaining these over prolonged periods of time with minimal side effects offer great opportunities for new product development, especially when using already FDA-approved drugs with well-known safety and efficacy. This special ocular drug delivery issue includes advances in ocular drug delivery technologies for both anterior and posterior segment diseases, while also highlighting the current challenges faced with regard to the ocular barriers present as well as the establishment of suitable models to reliably test the developed systems and thus avoid failure in clinical trials. Guest editors are Ilva Rupenthal and Michael O'Rourke.

Ilva Rupenthal received a B.Pharm. from Philipp University of Marburg, Germany, in 2003 and completed a Ph.D. on "Ocular Delivery of Antisense Oligonucleotides" with the School of Pharmacy and the Department of Ophthalmology, University of Auckland, in February 2008. In 2010, Ilva was awarded a three-year New Zealand Science and Technology Postdoctoral Fellowship to establish an ophthalmic pharmaceuticals group within the New Zealand National Eye Centre, with pharmaceutical scientists working alongside clinician-researchers to help translate cutting-edge eye research into clinical applications. Ilva was subsequently appointed as a senior lecturer and director of the Buchanan Ocular Therapeutics Unit (www.botu.nz) at the University of Auckland, New Zealand, which aims to translate ocular therapeutic-related scientific research into the clinical setting, whether pharmaceutical, cell, or technology based. Ilva's current research, cofunded by a Sir Charles Hercus Health Research Fellowship from the New Zealand Health Research Council, focuses predominantly on the development of stimuli-response ocular drug delivery systems, with projects investigating implants responsive to light or a small electrical current. Ilva's team, including six Ph.D. candidates, is also investigating other ocular therapeutics in the area of dry eye, diabetic retinopathy, and age-related macular degeneration management. Ilva is an author on over 40 scientific research publications and has attracted over NZ\$4.8 million in research funding. She has received several awards, including the Health Research Council 25th Anniversary Emerging Researcher Excellence Award in 2016 and the University of Auckland Early Career Research Excellence Award in 2014, while also winning Spark Entrepreneurship Ideas Challenges in 2012 and 2014 for her innovative ocular drug delivery ideas. Ilva is an active member of the Controlled Release Society and acts as a reviewer for a number of international pharmaceutical and ophthalmological journals as well as international funding bodies.



continued



Michael O'Rourke, president of Scotia Vision Consultants, has been involved in drug delivery for over 30 years across ophthalmology, periodontal, and pulmonary markets, including strategy development and global commercialization; previous companies include 3M Pharma, Pfizer, Alza, Chiron Vision, Bausch + Lomb, and GrayBug. Scotia Vision works with and advises ophthalmic companies on all aspects of commercialization and product development with a focus on anterior and posterior ocular drug delivery. Prior to establishing Scotia Vision Consultants in 2009, Michael was general manager for Bausch + Lomb's U.S. pharmaceuticals division in Tampa, Florida, with full P&L and operating responsibility, transforming the business to record levels of growth and managing 150 employees. Previously, he pioneered new Bausch + Lomb global strategy divisions, including pharmaceutical, drug delivery, and surgical products in California and New York. His ocular drug delivery experience includes launching the world's first intraocular drug delivery technology in Europe, Vitrasert[®], and the world's second, Retisert[®], in the United States. Michael was the first European marketing director for Chiron Vision Europe. Additional experience includes Alza

International (drug delivery), establishing their European division and launching the world's first sustained release technology treating periodontitis, Actisite[®]. At 3M, Michael worked in both sales and marketing for new sustained release therapeutics and enhanced aerosol delivery technologies treating pulmonary disease. Michael has managed 28 brands, led 13 product launches, structured/negotiated 12 strategic business deals, and been a team member in 18 device/drug approvals. Michael has both presented and published within ophthalmology at congresses and within respected journals. He is chairman of the foundation board for the Lions Eye Institute, a guest speaker on strategic planning at the University of Tampa, and was a part-time marketing lecturer at Trent University in Nottingham, United Kingdom. He is a native of Scotland and has lived and worked in Europe, the United States, and Asia. In 2010 he became a member of the GlobalScot business network, assisting Scottish-based life science companies in planning for U.S. market entry. He currently resides in Tampa, Florida (scotiavc@gmail.com, +1.813.323.1438, www.scotiavisionllc.com). ■

Celebrating 20 Years of Excellent Research and Translation

Dan Peer, Tel Aviv University, Israel

The 10th annual meeting of the CRS Israeli Local Chapter (ICRS), “20 Years of Excellent Research and Translation,” was held in Maalot, in the north of Israel, on September 14–16.

The conference attracted 220 attendees, including 100 graduate students and postdocs and 55 industry scientists and executives in addition to clinicians and faculty members.

Sessions focused on nanomedicines in cancer treatment; clinical oncology; advanced molecular imaging; innovative delivery vehicles; gene silencing and editing; new commercial technologies; theranostics, delivery science, and tissue engineering; advanced delivery strategies; and advanced formulations for targeting inflammation.

In addition, a panel of clinical oncologists and a panel of translational research experts (featuring venture capitals, faculty members who are also entrepreneurs, and company executives) discussed inventions and the translation from academia to industry.

The conference included five stellar plenary talks. Kinam Park (Purdue University, U.S.A.) spoke on “Drug Delivery Systems: Achieving Accelerated Evolution.” Philip Low (Purdue University, U.S.A.) presented “Ligand-Targeted Imaging and Therapeutic Agents for Multiple Human Diseases.” Alexander Kabanov (University of North Carolina, U.S.A.) addressed “Very High Capacity Polymeric Micelles for Drug Delivery.” Alan Packard (Harvard Medical School, U.S.A.) spoke on “PET Imaging: From Pico to Nano.” Finally, Patrick Couvreur (Paris-Sud University, France) presented “Nanotechnologies for the Treatment of Severe Diseases.”

The conference was organized and orchestrated by ICRS president Dan Peer together with ICRS treasurer Rosa Azhari. ■



From left to right: Yechezkel (Chezy) Barenholz (Hebrew University), Phil Low (Purdue University), Alan Packard (Harvard Medical School), Kinam Park (Purdue University), Alexander (Sasha) Kabanov (North Carolina University, Chapel Hill), Ronit Satchi-Fainaro (Tel Aviv University), Mark Behlke (Integrated DNA Technologies), Marina Dobrovolskaia (NIH/NCI), Marcelle Machluf (Technion), Dan Peer (Tel Aviv University), Rosa Azhari (Ort Brauda), Jason Dearling (Harvard Medical School), Avri Robinstein (Hebrew University), Patrick Couvreur (Paris Sud), and Simon Benita (Hebrew University).



Panel discussion “Translation: From Academia to Industry.”

MyCRS Symposium and Annual General Meeting at the Pharma+BioAsia Conference

Mohd Cairul Iqbal Mohd Amin, Universiti Kebangsaan Malaysia



MyCRS president Mohd Cairul Iqbal Mohd Amin presents the best poster award to Bencharwan Chamsai.

The CRS Malaysia Local Chapter (MyCRS) took part in Pharma+BioAsia 2016 as a Knowledge Partner. The meeting was held September 28–29 at the Kuala Lumpur Convention Centre, Kuala Lumpur, Malaysia. MyCRS’s role was to promote CRS as a whole in the conference and to organise a two-hour session, the MyCRS Symposium in the area of drug delivery and controlled release. MyCRS also sponsored a best poster award at the conference. The annual general meeting took place immediately after the symposium. MyCRS, which formed two and a half years ago, currently has 98 members.

The following MyCRS officers were elected for 2016–2018: Mohd Cairul Iqbal Mohd Amin, president; Ng Shiow Fern, deputy president; Farrukh Zeeshan, secretary; Mohd Hanif Zulfakar, treasurer; and Lik Voon Kiew, postgraduate representative. There is also a ten-member nonexecutive council.

Over the past year, MyCRS has held several events. First was a drug delivery seminar held in conjunction with the International Medical University (IMU) in September 2015. Second, MyCRS held a professional development workshop “Nanomedicine: Myth or Reality,” co-organised with IMU. Finally, at the end of August, MyCRS participated in the drug delivery seminar series held at the Faculty of Pharmacy, Universiti Kebangsaan Malaysia. The speaker was Claire Martin (School of Pharmacy, University of Wolverhampton, U.K.), who presented “Mucoadhesive Buccal Tablets Based on HPMC and Polaxamer 407 for Controlled Delivery of Chlorhexidine.” ■



Presenters at the MyCRS Symposium 2016.

Patent Watch

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

This article briefly summarizes novel aspects of selected United States (U.S.) patents involving controlled release or delivery that were issued from January 1 to June 30, 2016. Patents are loosely categorized into selected subject areas, but most have potentially broader applicability. Greater detail on each can be found on the U.S. patent website at <http://patft.uspto.gov/>.

Consumer and Diversified Products

U.S. patent 9,371,454 – Coating compositions containing amorphous aluminum phosphate are described for controlled release of phosphate anions to inhibit corrosion.

U.S. patent 9,357,865 – Encapsulated aromatic food additives are released in response to energy emitted from a nearby activation source associated with an eating utensil or oral insert.

U.S. patent 9,327,322 – Variations in sonic energy and reactants are used to control generation of active species for surface preparation, cleaning, or etching.

U.S. patent 9,307,692, 9,307,693, and 9,313,946 – Organosilane-coated magnetic nanoparticles are covalently bound in coatings for triggered release through magnetic stimulation in agricultural applications.

U.S. patent 9,296,661 – A controlled-release fertilizer composition/system that promotes more efficacious application of fertilizer through the use of root attractant and a root-attractant design is described.

U.S. patent 9,271,495 – Cationic biocidal materials are ion-paired with anionic molecules to form biocidal salts with controlled solubility that maintains minimal efficacious dissolved biocide concentrations over extended time periods.

U.S. patent 9,265,277 – A controlled release beadlet consisting of multiple carotenoids selectively positioned in coating layers is described to deliver individual carotenoids at preselected times in the gastrointestinal tract in a sequence that minimizes competitive uptake and maximizes individual carotenoid delivery.

Geometric/Shape Systems

U.S. patent 9,375,428 – Controlled release oral pharmaceutical compositions comprised of a polyethylene oxide/opioid matrix core surrounded by a coating with at least one opening through the coating provides zero order release of at least 80% of the opioid. Release is controlled by both the matrix erosion rate and geometric shape of the dosage form.

U.S. patent 9,308,168 and 9,370,574 – A biocompatible/absorbable/biodegradable/fiber-reinforced composite ring structure is described for controlled release of various bioactive molecules at intravaginal, intraperitoneal, or subcutaneous locations.

Hydrogels

U.S. patent 9,370,485 – A system involving *in situ* formation of a hydrogel for controlled release of suspended therapeutic agent at sites in and around the eye is disclosed.

Implants

U.S. patent 9,308,162 – Biocompatible oligomer-polymer compositions for injection/*in situ* formation of controlled release implants in the absence of undesired solvents are disclosed.

Materials

U.S. patent 9,295,643 – A solvent-free process of obtaining an insoluble fiber rich fraction from *Trigonella foenum-graceum* seeds is disclosed. The product can be used as a binder, disintegrant, filler, dispersing agent, or coating agent in controlled release pharmaceutical, food, or cosmetic formulations.

Miscellaneous

U.S. patent 9,370,525 and 9,351,975 – Controlled-release tablet preparations of oxcarbazepine and derivatives employ solubility and/or release enhancing agents to tailor sigmoidal release profiles for once-per-day dosing.

U.S. patent 9,364,553 – Biomolecule-polymer conjugates are employed to extend the availability of cleavable therapeutic bioactive fragments.

U.S. patent 9,327,076 – An electronically and remotely controlled pill consisting of a drug reservoir and electronically controlled valve or hatch for controlled drug delivery to the gastrointestinal tract is disclosed.

U.S. patent 9,308,170 and 9,308,171 – A polyethylene oxide gelling agent is employed as an abuse deterrent in immediate release opioid formulations.

U.S. patent 9,307,906 – A computer-controlled pain research sensory testing system is disclosed for controlled delivery of pressure, auditory, olfactory, and other bioactive stimuli and collection of feedback in relation to the stimuli.

Pulsatile Systems

U.S. patent 9,308,177 – Erodable, diffusion, and osmotic controlled release mechanisms are employed to provide single-dose pulsatile release of isosorbide dinitrate and hydralazine hydrochloride in the treatment of angina and related disease conditions.

Release Triggers

U.S. patent 9,248,894 – A corrosion release triggering system consisting of electrode clips that corrode to a failure point at a rate proportional to applied power is described.

Structural Manipulations

U.S. patent 9,351,934 – A gelatin matrix is crosslinked via heat treatment and degraded by gamma-ray irradiation treatment to create a support for controlled delivery of bioactive molecules.

U.S. patent 9,345,723 – A crosslinked composition of chitosan and guanosine 5'-diphosphate is disclosed as a tissue regeneration scaffold and controlled drug delivery structure.

U.S. patent 9,333,163 – Controlled mosaic patterns of functional drug-containing surface domains on nano- or micro-particles are described for controlled or sustained drug release.

U.S. patent 9,321,030 – Clay and organic polyanion film compositions built by layering strategies with incorporated cationic bioactive molecules such as antibiotics are described for controlled release of the bioactive.

U.S. patent 9,309,364 – Alkynyl aryl monomers with multiple terminal alkyne groups are coupled with iodo- or bromo-aryl monomers consisting of multiple halogen atoms in the presence of a palladium (0) catalyst to create a microporous polymer structure applicable to controlled release applications.

U.S. patent 9,289,437 – A system for covalently binding drug or drug-containing devices such as micelles or nanoparticles within a crosslinked polymer matrix is described for use in controlled drug delivery.

U.S. patent 9,260,803 – A method of electrospinning fibers with an inner bioactive containing core surrounded by a porous outer shell for controlled drug delivery is described.

U.S. patent 9,254,333 – Ultrasonication is used to rapidly encapsulate bioactive materials in silk fibroin hydrogel for controlled bioactive delivery.

U.S. patent 9,233,067 – A process to encapsulate bioactives in particles created from spider silk polypeptides for controlled delivery of pharmaceutical or cosmetic bioactives is described. ■

People in the News

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

Wallace K. Reams, Former President of Aveva Drug Delivery Systems, Joins Transdermal Delivery Solutions Board of Advisors

Business Wire: August 25, 2016 – PALM BEACH GARDENS, FL, U.S.A. – Transdermal Delivery Solutions Corporation (TDSC), www.TDSC.us, announced today that transdermal delivery veteran Wallace K. “Wally” Reams has joined its Board of Advisors.

Reams (www.linkedin.com/in/wreams) led the acquisition of Aveva Drug Delivery Systems Inc., a Florida-based developer and manufacturer of transdermal patches, for Nitto Denko Corporation, where as president and COO from 2003 to 2014 he successfully launched products for pain management, hypertension, antiemesis (resulting from chemotherapy), and smoking cessation.

“We are very pleased to have Wally Reams, a veteran transdermal delivery industry professional, join our Board of Advisors. His years of experience as COO of Aveva, as well as his reputation, relationships, and track-record of success in the pharmaceutical and medical device industries, will be an invaluable asset to our organization moving forward,” said Kenneth Kirby, president of TDSC.

Mr. Reams has 30+ years of experience in the pharmaceutical (transdermal drug delivery), medical device (wound care), and industrial products areas. He has demonstrated success in start-up and turnaround, new business development, strategic alliance, and development of high-quality senior management teams. He has extensive international experience, managing a strategic alliance in Japan, global distribution, and in his role of Directeur Général (president) of Brady SARL successfully led a turnaround and restructuring of a manufacturing and marketing company in Jouy-le-Potier, France.

“I am excited to join Ken and the TDSC team and look forward to helping move this paradigm-shifting platform technology to the market,” said Mr. Reams. “From my perspective of many years in development of patch-based transdermal delivery products, I can honestly say the HypoSpray® technology leaps past the state of the art and will enable delivery of compounds and classes of drugs not possible with patches. This has the potential to revolutionize medicine, and I am very pleased to be a part of it.”

TDSC is committed to advancing the science of transdermal drug delivery using its patented spray-on delivery system platform, HypoSpray®. TDSC’s proprietary system enables a much larger number of medications to be delivered directly through the skin, for systemic or localized application, utilizing its rapid acting, patchless, spray-on technology. TDSC’s technology represents a paradigm shift in drug delivery. www.tdsc.us/lower.php?url=tdsc-platform ■

Companies in the News

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

September

Chrono Therapeutics Raises \$47.6 Million in Series B Financing to Advance Its Clinical Platform for Personalized Drug Therapy

PRNewswire: September 8, 2016 – HAYWARD, CA, U.S.A. – Chrono Therapeutics, a pioneer in digital drug therapy and recent recipient of the World Economic Forum Technology Pioneer Award, today announced that it has closed a \$47.6 million series B financing. The round was led by Kaiser Permanente Ventures and included investments by Endeavour Vision, Xeraya Capital Labuan Ltd., Asahi Kasei, Emergent Medical Partners, Hikma Ventures, Cota Capital, and Mission Bay Capital. Chrono will use the funding to advance the clinical development of its smoking cessation platform and investigate other applications that can leverage its personalized drug therapy platform. In association with the financing, Liz Rockett, director of Kaiser Permanente Ventures, was named to Chrono Therapeutics' board of directors. Existing investors, including Canaan Partners, 5AM Ventures, Fountain Healthcare Partners, GE Ventures, and Mayo Clinic, participated in the round.

“Chrono Therapeutics’ platform has the potential to more effectively address nicotine addiction, a leading cause of death and illness around the world and a significant public health challenge,” said Rockett. “According to the CDC, over 40% of smokers try to quit each year, only a fraction of them succeed. We expect our investment to help Chrono achieve its mission to dramatically improve the tools that help people quit smoking.”

Chrono’s platform combines biologically timed drug delivery, embedded sensor technology to monitor compliance, and connected and personalized behavior change support. The platform’s first application tackles smoking cessation. Timed delivery of medication may offer benefits for other indications, including opioid addiction, Parkinson’s disease, and pain management.

“We have made tremendous progress in developing our technology to help people quit smoking, one of the lowest cost ways to improve health and reduce healthcare costs,” said Alan Levy, Ph.D., chairman and CEO of Chrono. “This financing will bring us closer to commercializing our system for smoking cessation and also enable us to dive more deeply into other applications where we can make a major impact and save lives.”

Chrono’s wearable transdermal drug delivery device times nicotine delivery to when smokers have their strongest cravings. Studies show that 75% of all smokers reach for their first cigarette within 30 minutes of waking up. The Chrono solution is designed to deliver the first dose of nicotine replacement therapy shortly before the smoker wakes up and to create a pattern of “peaks and troughs” of nicotine delivery throughout the rest of the day to ensure the smoker has more nicotine support when cravings are predicted to be strongest. In a recent clinical trial of adult male smokers, Chrono’s smoking cessation technology demonstrated a clinically meaningful and statistically significant reduction in nicotine cravings.

“Chrono’s technology is the first of its kind and holds the potential to significantly improve the way we provide an end-to-end patient-centered solution for those people struggling with addiction and chronic neurological diseases,” said Wende Hutton of Canaan Partners. “We welcome our new investors and look forward to the additional experience and perspective they will bring to Chrono. Kaiser Permanente Ventures’ insights into delivering value-based pharmaceutical offerings to managed care environments and Endeavour Vision’s experience in international markets will add significant value to this exciting company.”

Effective care of the most hard-to-treat conditions requires approaches beyond simply taking medicine. Chrono’s team is developing a next-generation transdermal drug delivery wearable that integrates biologically timed drug delivery with personalized digital support to help people achieve optimal clinical outcomes and lifestyle improvements. Chrono’s first application is in smoking cessation, enabling smokers to overcome the world’s deadliest addiction. For more information, visit www.chronothera.com.

Heron Therapeutics Announces Presentations of Results from Phase 2 Clinical Trial of HTX-011 in Hernia Repair at PAINWeek® 2016

Business Wire: September 8, 2016 – REDWOOD CITY, CA, U.S.A. – Heron Therapeutics, Inc. (NASDAQ:HRTX), a biotechnology company focused on improving the lives of patients by developing best-in-class medicines that address major unmet

medical needs, announced that results from the initial portions of Heron's phase 2 study of HTX-011 in patients undergoing inguinal hernia repair (Study 202) will be presented today in two posters at PAINWeek®, the national conference on pain for frontline practitioners, in Las Vegas, Nevada. The posters were coauthored by Harold S. Minkowitz, MD, Diplomate American Board of Anesthesiology, Department of Anesthesiology, Memorial Hermann Memorial City Medical Center, and Peter J. Winkle, MD, FACP, CPI, FACC, Anaheim Regional Medical Center, Anaheim Clinical Research.

Study 202 was a randomized, placebo-controlled, double-blind phase 2 clinical study in patients undergoing inguinal hernia repair. The study evaluated the efficacy and safety of three formulations of HTX-011 and two routes of administration into the wound (injection and instillation). Instillation into the incision site is an easier and potentially safer route of administration as it avoids multiple injections around the wound (as many as 10 or more in large operations) that carry the risk of venous puncture.

The primary endpoint was the difference as compared to placebo in pain intensity as measured by the summed pain intensity (SPI) score in the first 24 hours postsurgery (SPI 0–24). Important secondary endpoints included SPI for the first 48 hours postsurgery, total opioid consumption, and the percent of patients opioid-free through 96 hours postsurgery. Today's presentations describe part B of the study (202B), which compared our planned phase 3 formulation of HTX-011 (HTX-011B) at 200 mg ($n = 30$) and 400 mg ($n = 30$) to saline placebo ($n = 31$). The major findings for the 400 mg dose of HTX-011B as compared to placebo are as follows:

- There was a 29.5% reduction in pain as measured by SPI 0–24 ($p = 0.0035$).
- Instillation (29.9% reduction in SPI 0–24) was equally as effective as injection (29.1% reduction in SPI 0–24).
- The pain reduction was long lasting, with a statistically significant, 25.2% reduction through 48 hours (SPI 0–48; $p = 0.0250$).
- Mean total opioid consumption decreased by 22.4% through 96 hours postsurgery.
- The number of patients who were opioid-free through 96 hours postsurgery was substantially higher (24.1% versus 6.5%).

HTX-011 has been generally well tolerated in the ongoing phase 2 program, which has involved more than 250 administrations of HTX-011. In Study 202B, the frequency of treatment-related adverse events reported was 38.7% in the HTX-011B 200 mg group, 33.3% in the HTX-011B 400 mg group, and 51.6% in the placebo group. The most frequent treatment-related adverse events reported were nausea, constipation, and headache.

"I have been working in acute pain research for 25 years, and I have worked with many new products. I am extremely impressed with the efficacy of HTX-011," commented Harold S. Minkowitz, MD, Diplomate American Board of Anesthesiology, Department of Anesthesiology, Memorial Hermann Memorial City Medical Center. "Additionally, the unique ability to instill HTX-011 with equal efficacy to a standard infiltration technique provides a fast, easy, and safe route of administration."

"The results presented today give us confidence as we prepare for our broad-based phase 3 registration program," commented Barry D. Quart, PharmD, chief executive officer of Heron Therapeutics. "We remain focused on our goal of delivering a therapeutic tool that can not only greatly reduce pain levels following surgery but also reduce the burden of opioids."

Heron's posters from PAINWeek® 2016 are available on Heron's website (www.herontx.com) under Scientific Posters and Presentations under the following titles:

- Local Administration of HTX-011, a Long-Acting Biochronomer®-Based Bupivacaine/Meloxicam Combination, in Hernia Repair: Preliminary Results of an Interim Analysis
- Local Administration of HTX-011, a Long-Acting Biochronomer®-Based Bupivacaine/Meloxicam Combination, in Hernia Repair Provides Similar Initial Results Whether Injected or Instilled

HTX-011, which utilizes Heron's proprietary Biochronomer® drug delivery technology, is a long-acting formulation of the local anesthetic bupivacaine in a fixed-dose combination with the anti-inflammatory meloxicam for the prevention of postoperative pain. By delivering sustained levels of both a potent anesthetic and an anti-inflammatory agent directly to the site of tissue injury, HTX-011 was designed to deliver superior pain relief while potentially reducing the need for systemically administered pain medications such as opioids, which carry the risk of harmful side effects, abuse, and addiction. HTX-011 is the subject of a broad-based phase 2 development program designed to target the many patients undergoing a wide range of surgeries who experience significant postoperative pain.

Heron Therapeutics, Inc., is a biotechnology company focused on improving the lives of patients by developing best-in-class medicines that address major unmet medical needs. Heron is developing novel, patient-focused solutions that apply its innovative science and

technologies to already-approved pharmacological agents for patients suffering from cancer or pain. For more information, visit www.herontx.com.

DelMar Pharmaceuticals and Accurexa to Collaborate in the Development of a Novel Combination Chemotherapy for the Local Treatment of Brain Cancer

PRNewswire: September 7, 2016 – VANCOUVER, British Columbia, Canada, and WALNUT CREEK, CA, U.S.A. – DelMar Pharmaceuticals, Inc. (NASDAQ: DMPI) (“DelMar”), a company focused on developing and commercializing proven cancer therapies in new orphan drug indications, and Accurexa Inc. (OTCQB: ACXA) (“Accurexa”), a company focused on the development of novel neurological therapies to be directly delivered into the brain, announced today a collaboration to develop a novel formulation for the local delivery of combination chemotherapy for the treatment of brain cancer and other solid tumors.

Under the terms of the collaboration agreement DelMar will supply VAL-083 (dianhydrogalactitol) to be formulated within Accurexa’s proprietary ACX-31 implantable polymer wafer to locally deliver VAL-083 in combination with temozolomide and/or BCNU for the treatment of brain cancer. DelMar has been granted an exclusive option to license or acquire and commercialize product candidates and intellectual property resulting from the research.

Accurexa’s ACX-31 program has been developed in collaboration with Prof. Henry Brem, who built one of the largest brain tumor research and treatment centers in the world at Johns Hopkins University, and Prof. Robert Langer, who is the David H. Koch Institute Professor at MIT and the most cited engineer in history. Prof. Avi Domb at the Hebrew University of Jerusalem will lead the formulation development efforts for the collaboration. Profs. Brem, Langer, and Domb are pioneers in the development of local drug delivery treatments, and invented and developed Gliadel® (carmustine implant) which is an FDA-approved, local chemotherapy for the treatment of GBM. Drs. Brem and Langer will serve as advisors for the collaboration.

“Working together with Accurexa will allow DelMar to explore a promising new product opportunity that is complementary to our existing portfolio of systemic drug development programs established around VAL-083 without significant cash outlay or impact on our near-term cash burn rate,” said Jeffrey Bacha, chairman and CEO of DelMar Pharmaceuticals. “This research collaboration will take advantage of our knowledge regarding the unique cytotoxic mechanism of VAL-083 to deliver combination chemotherapy directly to patients’ cancer. Combining drugs with distinct mechanisms for local delivery provides an opportunity to overcome chemoresistance while minimizing potential systemic toxicity.”

“We are very pleased to collaborate with DelMar’s experienced team, allowing us to leverage their strong development capabilities. They have recently completed a phase I/II clinical trial of VAL-083 in brain cancer patients and had a successful end-of-phase II meeting with the FDA, while we recently had a positive pre-IND meeting with the FDA for our ACX-31 wafer program. Looking forward to the future development pathway, we believe that the local delivery of VAL-083 as a component of our ACX-31 wafer could potentially provide a new and exciting treatment option for brain cancer patients,” said George Yu, MD, Accurexa’s president and CEO.

DelMar and Accurexa believe that combining VAL-083 with temozolomide and/or BCNU within Accurexa’s proprietary drug delivery system may provide treatment advantages while limiting systemic toxicity.

VAL-083 is a first-in-class, small-molecule chemotherapeutic. In more than 40 phase I and II clinical studies sponsored by the U.S. National Cancer Institute, VAL-083 demonstrated safety and efficacy in treating a number of cancers including lung, brain, cervical and ovarian tumors and leukemia. VAL-083 is approved in China for the treatment of chronic myelogenous leukemia and lung cancer and has received orphan drug designation in the United States for the treatment of gliomas, medulloblastoma, and ovarian cancer as well as in Europe for the treatment of glioma.

VAL-083 exhibits its antitumor effect by forming DNA cross-links at the N7 position of guanine, whereas temozolomide and BCNU primarily target the O6 position of guanine as their site of anticancer function.

VAL-083’s mechanism of action appears to be unaffected by the expression of MGMT, a DNA repair enzyme that causes chemotherapy resistance to chemotherapies targeting the O6 position of guanine. DelMar has also demonstrated that the combination of VAL-083 and temozolomide was highly effective against brain tumor stem cells *in vitro*.

DelMar and Accurexa will seek to establish a novel formulation that incorporates VAL-083 into the ACX-31 polymer wafer and to establish nonclinical proof of concept regarding the proposed advantages of the combination therapy. DelMar will supply Accurexa with VAL-083, and the companies will share certain limited costs associated with the research. DelMar has been granted an exclusive

option to license or acquire and commercialize product candidates and intellectual property resulting from the research for a defined period after the completion of the research. DelMar's option to negotiate a license or acquire the technology includes any and all results, research materials, related information, and product candidates, including without limitation ACX-31 and related intellectual property and all rights thereto on an exclusive worldwide basis or other such terms as the parties may agree, in order to further develop and commercialize products based on the research project.

"Both of our companies have already made significant investments into the IP, mechanism of action, and formulation of VAL-083 and ACX-31, respectively. Therefore, developing a combined formulation is not expected to require significant cash expenditures. This collaboration is a highly cost-effective approach to expand our product development portfolio by leveraging our companies' respective capabilities and assets," stated Mr. Bacha.

DelMar Pharmaceuticals, Inc., was founded to develop and commercialize proven cancer therapies in new orphan drug indications where patients are failing or have become intolerant to modern targeted or biologic treatments. The company's drug in development, VAL-083, is currently undergoing clinical trials in the United States as a potential treatment for refractory glioblastoma multiforme. VAL-083 has been extensively studied by U.S. National Cancer Institute and is currently approved for the treatment of chronic myelogenous leukemia (CML) and lung cancer in China. Published preclinical and clinical data suggest that VAL-083 may be active against a range of tumor types via a novel mechanism of action that could provide improved treatment options for patients. For further information, please visit <http://delmarpharma.com>.

Crescita Therapeutics™ Inc. Announces Acquisition of INTEGA Skin Sciences

PRNewswire: September 1, 2016 – MISSISSAUGA, Ontario, Canada – Crescita Therapeutics Inc. (TSX: CTX) (Crescita or the company), a drug development company that owns topical products for use in the treatment of medical conditions related to dermatology and pain, today announced that it has acquired INTEGA Skin Sciences Inc. (INTEGA), a Montreal-based dermatology company that develops, manufactures, sells, and markets science-based quality skin care products. INTEGA, financially backed by Knight Therapeutics (TSX: GUD) and Bloom Burton Healthcare Lending Trust, owns the Canadian distribution rights for a number of well-known and established skin care brands, including Laboratoire Dr. Renaud.

Key benefits of the transaction:

- Provides Crescita with a revenue-generating, fully integrated commercial skin care business, manufacturing facilities, and the capability to market prescription and over-the-counter (OTC) skin care products through established distribution channels;
- Provides Crescita with distribution rights to well-known and established skin care brands: Laboratoire Dr. Renaud, Pro-Derm, Premiology, and ISDIN;
- Provides Crescita with a commercial infrastructure capable of promoting its prescription drug Pliaglis in Canada;
- Allows Crescita to leverage its topical delivery technologies for the development of potential new OTC and/or prescription skin care products;
- Allows Crescita to leverage its business development capabilities to out-license INTEGA-owned brands outside Canada, including the United States; and
- Significant cash on hand in order to make additional acquisitions.

"With the acquisition of INTEGA, paid in Crescita common shares valued at \$2.44 per share, Crescita becomes an integrated commercial skin care company while maintaining a strong balance sheet to finance our continued growth," commented Dan Chicoine, Crescita's chairman. "Our goal is to utilize the combined attributes of both businesses, in manufacturing, distribution, marketing, and research and development, to become a dominant player in the \$15.0 billion Canadian and U.S. skin care industry."

"I am thrilled to be integrating INTEGA into Crescita as the first step to becoming a leading dermatology specialty pharmaceutical company," said Greg Orleski, founder and CEO of INTEGA.

Jonathan Goodman, CEO of Knight Therapeutics, added, "As shareholders of INTEGA and now Crescita, we are supportive of this acquisition. We believe that INTEGA's established commercial brands and unique distribution capabilities combined with Crescita's technology, experienced management, and strong balance sheet will facilitate accelerated organic growth and support future consolidation opportunities."

Crescita (TSX: CTX) is a publicly traded Canadian drug development company that owns topical products for treating medical conditions in dermatology and pain. Crescita owns multiple proprietary drug delivery platforms that support the development of

patented formulations that can facilitate the delivery of active drugs into or through the skin. Crescita's board of directors and management team have demonstrated success in building Crescita's predecessor company, Nuvo Research Inc., including developing multiple drugs that are now approved and commercialized and negotiating multiple licensing transactions. For additional information, please visit www.crescitherapeutics.com.

August

Caisson Biotech Seeks Buyer for HEPtune® Drug-Delivery Platform

Business Wire: August 31, 2016 – AUSTIN, TX, U.S.A. – Caisson Biotech, LLC, has engaged Pickwick Capital Partners, LLC (member FINRA/SIPC), to assist in the sale of the HEPtune® drug-delivery platform. The proprietary platform centers on the use of a naturally occurring sugar polymer, heparosan, which is produced by the body and is naturally biodegradable. The platform includes a robust U.S. and international patent portfolio and has been proven in hemophilia. Additional opportunities are potentially available in a range of established, billion-dollar biologic therapeutics markets, as well as for improved delivery of small molecules via nanocarriers.

“The sale is designed to accelerate broad industry adoption of heparosan and deliver its clinical benefits to the maximum number of patients possible,” Caisson said.

“Caisson's HEPtune® platform has been demonstrated to improve proteolytic activity and half-life for hemophilia factor VII compared with unconjugated FVII or FVII conjugated with polyethylene glycol (PEG). Additionally, HEPtune enables new patent protection for drug conjugates, can lower costs, and reduce the growing concern of immunogenicity with PEG conjugates,” said Paul Bundschuh, a managing director at Pickwick Capital Partners. “Many therapeutic protein market opportunities exist that could benefit from HEPtune. Pickwick is excited to leverage our life sciences/biotech team of experienced bankers and subject-matter experts to help Caisson find the ideal buyer/s.” For questions regarding the sale of the HEPtune platform, contact Paul Bundschuh, bundschuh@pickwickcapital.com.

HEPtune was developed by Caisson and Dr. Paul DeAngelis, at the University of Oklahoma. Visit www.caissonbiotech.com.

Caisson is funded and managed by Austin-based Emergent Technologies, Inc. Visit www.emergenttechnologies.com.

Pickwick Capital Partners, LLC, helps innovative companies in the lower middle-market achieve their strategic objectives through M&A and capital raising. Visit www.pickwickcapital.com.

NLS Pharma Announces Start of Its Phase 2 Trial for Mazindol in Adult ADHD Patients

PRNewswire: August 29, 2016 – STANS, Switzerland, Aug. 29, 2016 – NLS Pharma Group (NLS) announced today that it has initiated enrollment for its “Double-Blind Placebo-Controlled Phase II 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 first patient in marks an important milestone in the development of a non-amphetaminic stimulant for ADHD,” said Alex Zwyer, CEO at NLS Pharma Group.

Mazindol is a wake-promoting agent, a norepinephrine and dopamine reuptake inhibitor that was previously approved as an immediate release (IR) formulation in Europe and in the United States for the short-term treatment of obesity. It was taken off the market for reasons unrelated to its efficacy and safety. Rebalancing dysfunctional central nervous system (CNS) noradrenergic and dopaminergic systems appears to be critical for the effective treatment of ADHD and narcolepsy. Given that the central nervous system (CNS) noradrenergic and dopaminergic systems appear to be dysfunctional in ADHD and that an open-label trial of mazindol demonstrated efficacy in improving the symptoms of pediatrics with ADHD, NLS is developing a controlled release (CR) formulation of mazindol to potentially treat this disorder.

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

“As only a fraction of adults with ADHD are being treated with traditional stimulants, it is clear that alternatives are needed. ADHD can affect numerous aspects of a patient's life, and the current phase II study is examining functional outcomes in order to determine

the impact of treatment,” according to Dr. Tim Wigal, lead investigator. “Depending on the results in adults, this line of research may quickly expand to include younger patients.”

Nelson Handal, MD, chief medical officer of NLS, said, “Clinicians and patients need effective and tolerable nonstimulant alternative medications to treat ADHD. Additionally, at-risk populations need safe and nonaddictive treatment options. This study creates a unique opportunity for the safe and successful treatment of ADHD in adults.”

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

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

On July 11, 2016, NLS announced that the U.S. Food and Drug Administration (FDA) had granted Orphan Drug Designation (ODD) for mazindol for the treatment of narcolepsy. On October 9, 2015, an ODD was granted by the European Commission to NLS for mazindol within the same indication. Series A financing was successfully completed on August 31, 2015, to secure full development of NLS-1 (mazindol) up to proof-of-concept in ADHD.

Egalet Announces Scientific Presentations at PAINWeek 2016 Meeting

PRNewswire: August 25, 2016 – WAYNE, PA, U.S.A. – Egalet Corporation (Nasdaq: EGLT) (“Egalet”), a fully integrated specialty pharmaceutical company focused on developing, manufacturing, and commercializing innovative treatments for pain and other conditions, today announced that researchers will present scientific data at PAINWeek 2016 on September 8 in Las Vegas. Four presentations will be on abuse-deterrent product candidate ARYMO™ ER (morphine sulfate) extended-release tablets; one presentation will address abuse-deterrent properties of Egalet’s proprietary Guardian™ technology; and one presentation will be on marketed product OXAYDO® (oxycodone HCl, USP) tablets CII.

ARYMO ER was developed for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. ARYMO ER uses Egalet’s proprietary Guardian™ technology, a polymer matrix tablet technology that is combined with a novel application of the manufacturing process of injection molding. This results in tablets with controlled-release properties as well as physical and chemical features that have been demonstrated to resist both common and rigorous methods of manipulation, in order to deter common routes of abuse. OXAYDO is an immediate-release oral formulation of oxycodone HCl indicated for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate. In addition, it is also the only approved immediate-release opioid designed to discourage abuse via snorting.

“Our presentations at PAINWeek will highlight the breadth of data on our product candidate ARYMO ER, which uses Egalet’s Guardian™ technology to achieve both abuse-deterrent and extended-release properties,” said Jeffrey Dayno, MD, Egalet’s chief medical officer. “In addition, we also will present results from category 1 abuse-deterrent experiments with OXAYDO, which assessed the challenges of syringeability and potential for abuse deterrence via the intravenous route of administration. We look forward to sharing these data with attendees at the upcoming PAINWeek conference.”

The following posters will be presented during the PAINWeek 2016 poster session on Thursday, September 8, from 7:00 to 9:00 pm:

- Pharmacodynamic Effects from a Category 3 Oral Human Abuse Potential Study of an Abuse-Deterrent, Extended-Release Morphine Product Candidate in Nondependent, Recreational Opioid Users. Authors: Michael D. Smith, PharmD, Lynn R. Webster, MD, John Lawler, BS, Karsten Lindhardt, MSc, PhD, DBE, Jeffrey M. Dayno, MD.
- Pharmacodynamic Effects from a Category 3 Intranasal Human Abuse Potential Study of an Abuse-Deterrent, Extended-Release Morphine Product Candidate in Nondependent, Recreational Opioid Users. Authors: Lynn R. Webster, MD, Michael D. Smith, PharmD, John Lawler, BS, Karsten Lindhardt, MSc, PhD, DBE, Jeffrey M. Dayno, MD.
- Dissolution Studies in the Presence of Alcohol with an Abuse-Deterrent, Extended-Release Morphine Product Candidate. Authors: Torben Elhauge, MSc, Lene Kristensen, MSc, Karsten Lindhardt, MSc, PhD, DBE, Jeffrey Dayno, MD.
- Bioequivalence and Food Effect of a Novel, Abuse-Deterrent (AD), Extended-Release (ER) Morphine Product Candidate Compared with a Currently Available Non-AD, ER Morphine Product. Authors: John Lawler, BS, Gwendolyn Niebler, DO, Karsten Lindhardt, MSc, PhD, DBE, Jeffrey M. Dayno, MD.

- Injection Resistance of an Immediate-Release Oral Oxycodone Hydrochloride Product with Abuse-Deterrent Properties. Authors: Torben Elhauge, MS, Edward J. Cone, PhD, August R. Buchhalter, PhD, Jeffrey M. Dayno, MD, Karsten Lindhardt, MSc, PhD, DBE.
- Correlating Viscosity and *In Vitro* Dissolution to *In Vivo* Pharmacokinetic Profiles of Proprietary Injection-Molded Tablet Formulations with Abuse-Deterrent Characteristics. Authors: Nikolaj Skak, MS, Torben Elhauge, MS, Martin Jan Øvergård, ELT, Karsten Lindhardt, MSc, PhD, DBE.

Egalet, a fully integrated specialty pharmaceutical company, is focused on developing, manufacturing, and commercializing innovative treatments for pain and other conditions. Egalet has two approved products: OXAYDO® (oxycodone HCl, USP) tablets for oral use only CII, and SPRIX® (ketorolac tromethamine) nasal spray. In addition, using its proprietary Guardian™ technology, Egalet is developing a pipeline of clinical-stage product candidates that are specifically designed to deter abuse by physical and chemical manipulation. The lead programs, ARYMO™ ER, an abuse-deterrent, extended-release, oral morphine formulation, and Egalet-002, an abuse-deterrent, extended-release, oral oxycodone formulation, are being developed for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Egalet's Guardian technology can be applied broadly across different classes of pharmaceutical products and can be used to develop combination products that include multiple active pharmaceutical ingredients with similar or different release profiles. For additional information on Egalet, please visit egalet.com. For full prescribing information on SPRIX, including the boxed warning, please visit sprix.com.

Mayne Pharma Acquires Rights to a Portfolio of Dermatology Foam Products Including Fabior® and Sorilux®

Business Wire: August 18, 2016 – GREENVILLE, NC, U.S.A. – Mayne Pharma (ASX: MYX) is pleased to announce it has acquired a portfolio of on-market dermatology foam assets from GSK for US\$50.1 million. The foam assets include U.S. rights to Fabior and Sorilux, Canadian rights to Luxiq® and Olux-E®, and Mexican rights to betamethasone foam. Under the terms of the agreement, Mayne Pharma will acquire the approved regulatory filings, trademarks, marketing materials, select product inventory, and related medical and technical data and will acquire or obtain licenses for related patents.

Fabior (tazarotene) foam, 0.1% is a patent-protected topical product indicated for the treatment of acne, the largest dermatology indication in the United States, affecting up to 50 million Americans every year. Sorilux (calcipotriene) foam, 0.005% is a patent-protected topical product indicated for mild to moderate plaque psoriasis affecting up to 6 million Americans each year.

Both Fabior and Sorilux will be marketed through Mayne Pharma's Specialty Brands Division and existing sales team. Relaunch for both products is expected in FY17. During the intervening period, GSK will continue to distribute Fabior and Sorilux under a transition services arrangement.

The non-U.S. dermatology assets will continue to be distributed by GSK in the short term, and Mayne Pharma will seek to out-license these products to new partners.

Mayne Pharma's CEO, Mr. Scott Richards, said, "This acquisition will strengthen Mayne Pharma's position in the U.S. dermatology market, diversify future branded earnings, and create new opportunities for growth. Both Fabior and Sorilux are a strategic fit with the existing Doryx franchise and participate in attractive and growing markets. We believe both products are differentiated assets with compelling clinical data that physicians and patients will appreciate."

"Mayne Pharma is very attracted to the underlying fundamentals of the U.S. dermatology market. The acquisition will leverage existing commercial infrastructure across functions including sales and marketing, customer service, compliance, medical affairs, and contracts administration. We also expect to leverage the new foam capability in future branded and generic product development programs."

Mayne Pharma expects the products to contribute modest incremental EBITDA in FY17 and have significant potential for growth in future years.

Mayne Pharma is an ASX-listed specialty pharmaceutical company that develops and manufactures branded and generic products globally—either directly or through distribution partners—while applying its drug delivery expertise for contract development and manufacturing services.

Mayne Pharma has a 30-year track record of innovation and success in developing new oral drug delivery systems, and these technologies have been successfully commercialized in numerous products that have been marketed around the world.

Mayne Pharma has two drug development and manufacturing facilities based in Salisbury, Australia, and Greenville, NC, U.S.A., with expertise in formulating complex oral dose forms including highly potent compounds, controlled substances, modified release products, and inherently unstable compounds.

Juniper Pharmaceuticals Reports Results from Phase 2b Clinical Trial of COL-1077 Lidocaine Vaginal Gel in Gynecologic Procedure Pain

PRNewswire: August 17, 2016 – BOSTON, MA, U.S.A. – Juniper Pharmaceuticals, Inc. (Nasdaq: JNP) (“Juniper” or the “company”), a women’s health therapeutics company, today announced that a recently completed phase 2b clinical trial evaluating its 10% lidocaine bioadhesive vaginal gel, COL-1077, for the reduction of pain intensity in women undergoing an endometrial biopsy with tenaculum placement did not achieve its primary and secondary endpoints. The safety and pharmacokinetic (PK) profiles of COL-1077 were consistent with what has been observed in prior clinical trials of the lidocaine bioadhesive vaginal gel.

“We are disappointed that COL-1077 did not achieve the desired effect in this clinical trial. We believe the study was well-designed and -conducted and has adequately tested our hypothesis,” said Dr. Bridget A. Martell, Juniper’s chief medical officer. “On behalf of the Juniper team, I want to thank the patients and investigators who participated in this study.”

“Based on the results of this trial, we are discontinuing development of COL-1077,” said Alicia Secor, chief executive officer. “We will focus Juniper’s resources on our differentiated intravaginal ring (IVR) technology to advance our pipeline of product candidates to address unmet needs in women’s health.”

Juniper’s IVR programs are led by JNP-0101, an investigational oxybutynin IVR for the treatment of overactive bladder (OAB) in women. Roughly nine million women receive pharmacotherapy for this chronic condition in the United States alone. IND-enabling animal PK studies are underway, and the company expects pilot study results later this year.

“We expect to fund our operations and planned R&D activities with cash flows generated by our core business. We expect ongoing strong performance from the Crinone® franchise and Juniper Pharma Services,” Ms. Secor added.

“We remain committed to delivering value-added treatments that meet the unique and underserved healthcare needs of women,” Ms. Secor concluded.

Juniper Pharmaceuticals, Inc., is focused on developing therapeutics that address unmet medical needs in women’s health. The company is advancing a pipeline of proprietary product candidates that leverage novel intravaginal drug delivery technologies and the 505(b)(2) regulatory pathway. Juniper’s core operating business includes the Crinone® (progesterone gel) franchise and Juniper Pharma Services, which provides high-end fee-for-service pharmaceutical development and clinical trials manufacturing to clients. Please visit www.juniperpharma.com for more information.

Juniper Pharmaceuticals™ is a trademark of Juniper Pharmaceuticals, Inc., in the United States and European Union.

Crinone® is a registered trademark of Merck KGaA, Darmstadt, Germany, outside the United States and of Allergan, Inc., in the United States.

Oculis Completes Series A Financing

Business Wire: August 16, 2016 – REYKJAVIK, Iceland – Oculis announced today the close of a Series A financing round, led by Brunnur Ventures and Silfurberg. The new capital will support continued development of the company’s patented solubilizing nanoparticle (SNP) drug delivery platform and the company’s drug candidates, including the first topical eye drops for treatment of diabetic macular edema.

Oculis’ SNP platform technology is specifically designed to solve the limitations of available eye-drop technologies. The SNP technology is based on the combined efforts of Oculis’ founders, Dr. Thorsteinn Loftsson, a leading scientist in the field of cyclodextrin based drug delivery, and Dr. Einar Stefansson, a leading ophthalmologist in the field of diabetic eye disease. Oculis’ founders have over a course of 20 years made step-by-step improvements on eye-drop technologies, with the invention of the solubilizing nanoparticles being a major breakthrough.

The SNP technology allows for treatment of retinal diseases with topically administered eye drops, as has been demonstrated in four different clinical trials. The SNP technology substantially enhances solubility of lipophilic drugs and provides sustained release over

several hours compared with only a few minutes with conventional eye-drop technologies. The SNP technology has the potential to significantly improve eye drops, not only by allowing retinal delivery but also for anterior segment use.

To date, SNP containing various different drugs have been developed and tested, including SNP containing drugs for treatment of diseases in both the posterior and the anterior segment of the eye, such as steroids, nonsteroidal anti-inflammatory drugs, anti-VEGF drugs, angiotensin II receptor antagonists, carbonic anhydrase inhibitors, and peptides.

Oculus is looking to get DexNP, the company's most advanced drug candidate, approved as a treatment for diabetic macular edema (DME) in the United States and Europe. Approved DME drugs are invasive, either intravitreal injections or implants, with a large unmet medical need for noninvasive DME treatment options. Today, only a small part of the estimated 25 million global DME patients are receiving drug treatment, demonstrating the large unmet medical need. Two phase II trials conducted in Japan have demonstrated DexNP to be safe and effective as a treatment for DME, providing similar improvement in vision and central macular thickness (CMT) as approved invasive treatments. DexNP has substantial potential for expansion into other indications, including as a once-a-day postoperative anti-inflammatory treatment, as a treatment for uveitis, and as a complementary treatment for wet AMD.

Oculus has other promising product candidates under development in key ophthalmic indications, including wet AMD, glaucoma, dry eyes, and diabetic retinopathy.

"We are delighted to receive this support from Brunnur Ventures, Silfurberg and their co-investors to progress our development of DexNP. The investment will also allow us to further advance the SNP drug delivery platform and move forward other pipeline drug candidates in key ophthalmic indications," said Páll Ragnar Jóhannesson, CEO of Oculus. "In addition to providing financial resources, these experienced investors bring Oculus a wealth of operational and industry expertise. The investment is yet another recognition for the outstanding research work of Dr. Loftsson and Dr. Stefansson."

"Our investment to support the development of Oculus is based on Oculus's strong scientific research, combined with a great market potential for the company's drug candidates. The option of drug treatment of DME with self-administered eye drops, rather than having the only option of surgically injecting drugs into the eye, would be a major advantage in the global battle with this common and severe diabetes complication," commented Arni Blöndal of Brunnur Ventures. "We look forward to working with Oculus to translate its research into important new medicines."

In connection with the financing, Árni Blöndal of Brunnur Ventures and Stefan Jökull Sveinsson, former global head of R&D at Actavis, will join the Board. Other directors include Joseph Markoff, former global director for ophthalmology at Merck & Company and director at Wills Eye, James D. Pipkin, VP of new product development at Ligand Pharmaceutical, K. George Mooney, former VP of exploratory portfolio development at Pfizer, and Oculus's founders Dr. Loftsson and Dr. Stefansson, who serves as chairman of the board.

Oculus (www.oculispharma.com) is a clinical-stage, privately held pharmaceutical development company focusing on ophthalmic drugs and novel drug delivery to the eye. Oculus has developed the solubilizing nanoparticle (SNP) drug delivery platform consisting of a novel technique to facilitate drug absorption to both anterior and posterior parts of the eye. The SNP platform provides sustained release over several hours and allows for greatly increased solubility of lipophilic drugs. Among the key advantages of the SNP platform is a drug delivery system in which diseases of the posterior part of the eye can be treated with a simple topical application (i.e., an eye drop).

Nemaura Pharma Limited Awarded the Prestigious 2016 Frost & Sullivan Award for Best Practices in Enabling Technology Leadership in Transdermal Drug Delivery

Business Wire: August 15, 2016 – LOUGHBOROUGH, England – Nemaura Pharma has been awarded the prestigious 2016 Frost & Sullivan award for best practices in enabling technology leadership in the transdermal drug delivery industry.

The analysts stated that "Nemaura Pharma's drug delivery technology has revolutionized the way drugs are delivered in the healthcare system." They spoke highly of Nemaura's Memspatch liquid delivery system because it is highly accurate, easy to use, and patient-friendly. The Memspatch uses microneedle technology to insert several small needles no more than few millimetres into the skin. The dose is dispersed over a larger surface area than is possible with a single needle, facilitating faster absorption. The judges pointed out that Nemaura has overcome the problem of erratic dosing that has dogged traditional transdermal patches by adding an applicator to the system; this allows for 100% needle penetration.

“Conventional liquid vaccine has contamination and stability risks associated with it,” said Frost & Sullivan senior research analyst Debarati Sengupta. “Nemaura Pharma has reformulated the liquid vaccine into a stable, solid dose formulation, without any loss of potency.” The Micro-Patch system works by inserting a super-sharp stainless steel needle into the outer layer of the skin. The needle then retracts completely, minimising the risk of stick injuries, and the solid dose formulation remains deposited in the skin. The judges noted that the system eliminates the need for cold-chain storage, which should lead to significant savings and does not require a specialist to use it to administer the drug.

“The solid and liquid microneedle-based drug delivery technologies (Memspatch and Micro-Patch) provide pain-free, minimally invasive drug delivery with controlled drug dosage,” noted Debarati. “With superior drug absorption, reduced or minimal drug stability or dosage issues, this easy-to-use transdermal technology drives better patient compliance and outcomes. With its strong overall performance, Nemaura Pharma has earned Frost & Sullivan’s 2016 Enabling Technology Leadership Award.”

The award was made after an in-depth evaluation by Frost & Sullivan analysts, including a review by a panel of industry experts. “We are delighted and honoured to receive this accolade,” said Dr. Faz Chowdhury, CEO of Nemaura Pharma. “We have worked over several years to carefully integrate human factors into what we envisage will become the world’s leading injectable devices for a very wide range of drugs, and we anticipate this will enable patients globally to benefit from less intrusive and more intuitive devices for the routine administration of vaccines and medicines.”

A private specialist biotech company, Nemaura Pharma is strategically positioned to work with global pharmaceutical companies, as well as new biotechnology companies, to successfully bring both new and old drugs to patients in superior delivery formulations and systems. Ultimately, we aim to improve patient lifestyle and quality of life. Our advanced drug delivery systems are designed to increase the effectiveness and safety of therapeutic drugs, while also reducing complications due to patient noncompliance, and mitigating the side effects of less efficient delivery systems. For more information, please visit www.nemaura.co.uk.

TARIS Biomedical® Launches Second Phase 1b Clinical Trial of TAR-200 (GemRIS™) in Patients with Bladder Cancer

Business Wire: August 10, 2016 – LEXINGTON, MA, U.S.A. – TARIS Biomedical, 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™, gemcitabine releasing intravesical system) in patients with non-muscle-invasive bladder cancer (NMIBC). The study, which is being conducted in Europe, is the second phase 1b trial of TAR-200 in bladder cancer. TARIS announced the initiation of a study in muscle-invasive bladder cancer (MIBC) in July 2016. TAR-200, a drug-device combination product utilizing the TARIS® system, is designed to release gemcitabine continuously into the bladder over 7 days.

“Non-muscle-invasive bladder cancer, which represents 70–75% of newly diagnosed cases, is a serious disease with a profound impact on the lives of patients. The current management of this cancer includes repeated surgical and pharmacological interventions, as well as lifelong monitoring. Despite these efforts, many patients are still at risk of recurrence and, in some cases, progression to MIBC,” said Christopher J. Cutie, MD, chief medical officer of TARIS. “TAR-200 may ultimately offer a unique nonsurgical approach in the management of this disease.”

“The initiation of a second study of TAR-200 is another substantial milestone for our organization,” said Purnanand Sarma, Ph.D., president and chief executive officer of TARIS. “If successful, these two studies are designed to demonstrate the potential utility of TAR-200 across the entire spectrum of bladder cancer. We are very excited to advance these programs into the clinic and look forward to the results.”

The phase 1b open-label study will assess whether continuous, local exposure to gemcitabine using TAR-200 is safe and tolerable in patients with intermediate risk NMIBC. The study will also assess the preliminary efficacy and pharmacokinetics in this patient population. The study will be conducted at multiple sites in Europe and expects to enroll up to 30 patients after the diagnosis of NMIBC and before transurethral resection of bladder tumors (TURBT).

TAR-200 (GemRIS™) is TARIS’s first product candidate 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, bladder cancer exceeds all other forms of cancer. The estimated U.S. national expenditure on bladder cancer was \$4.3 billion in 2014.

Non-muscle-invasive bladder cancer (NMIBC) represents 70–75% of newly diagnosed cases. NMIBC tumors are confined to the innermost layers of the bladder wall and have not progressed into the deeper muscle layer or beyond. These tumors are currently managed using local resection (transurethral resection of bladder tumors or TURBT) and local pharmacological intervention. While current treatments often eliminate the existing tumor(s), the disease frequently recurs, requiring lifelong monitoring and repeated intervention. Further, higher-risk tumors that recur or progress despite these therapies often require patients to undergo radical cystectomy (complete surgical removal of the bladder). Radical cystectomy is a major, life-changing procedure, and many patients are medically unfit and/or unwilling to undergo this surgery.

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.

Heron Therapeutics Announces U.S. FDA Approval of SUSTOL® (Granisetron) Extended-Release Injection for the Prevention of Chemotherapy-Induced Nausea and Vomiting

Business Wire: August 10, 2016 – REDWOOD CITY, CA, U.S.A. – Heron Therapeutics, Inc. (NASDAQ: HRTX), today announced that the U.S. Food and Drug Administration (FDA) has approved SUSTOL® (granisetron) extended-release injection. SUSTOL is a serotonin-3 (5-HT₃) receptor antagonist indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.

SUSTOL is an extended-release, injectable 5-HT₃ receptor antagonist that utilizes Heron's Biochromer® polymer-based drug delivery technology to maintain therapeutic levels of granisetron for ≥5 days, covering both the acute and delayed phases of chemotherapy-induced nausea and vomiting (CINV).

“Despite advances in the management of CINV, up to half of patients receiving chemotherapy can still experience CINV, with delayed CINV being particularly challenging to control,” commented Ralph V. Boccia, MD, FACP, medical director, Center for Cancer and Blood Disorders. “In our experience, other 5-HT₃ receptor antagonists, including palonosetron, are generally effective for 48 hours or less. SUSTOL, due to its extended-release profile, represents a novel option that can protect patients from CINV for a full 5 days.”

The SUSTOL global phase 3 development program was comprised of two large guideline-based clinical trials that evaluated SUSTOL's efficacy and safety in more than 2,000 patients with cancer. SUSTOL's efficacy in preventing nausea and vomiting was evaluated in both the acute phase (day 1 following chemotherapy) and the delayed phase (days 2–5 following chemotherapy).

“The SUSTOL clinical trial populations and results are highly representative of cancer patients in our real-world clinical practice,” said Jeffrey Vacirca, MD, FACP, chief executive officer and director of clinical research, North Shore Hematology Oncology Associates, and vice president, Community Oncology Alliance. “Use of MEC regimens is widespread, and AC-based regimens are among the most commonly prescribed highly emetogenic chemotherapy regimens. The most significant challenge for my breast cancer patients receiving AC is chemotherapy-induced nausea and vomiting. SUSTOL represents a better option to manage this devastating side effect of therapy.”

“We would like to thank the investigators, caregivers, and most of all the patients who have helped us to achieve this important milestone,” commented Barry D. Quart, PharmD, chief executive officer of Heron Therapeutics. “In addition to bringing an important product to patients, we are extremely pleased to have obtained the first approval of a product utilizing Heron's Biochromer polymer-based drug delivery technology.”

“The approval of SUSTOL is a major step in Heron's evolution into a fully integrated biopharmaceutical company with both development and commercial capabilities,” said Robert H. Rosen, president of Heron Therapeutics. “Our focus now turns to ensuring patients have access to this important therapy. We look forward to collaborating with the oncology community to make SUSTOL available in the fourth quarter of this year.”

Intec Pharma to Pursue Development of Accordion Pill for Cannabinoid Therapies

Business Wire: August 4, 2016 – JERUSALEM, Israel – Intec Pharma Ltd. (Nasdaq: NTEC), a clinical stage biopharmaceutical company focused on developing drugs based on its proprietary Accordion Pill™ platform technology, announces the initiation of a new clinical development program for its Accordion Pill platform with the two primary cannabinoids contained in *Cannabis sativa*. Intec Pharma plans to formulate and test cannabidiol (CBD) and tetrahydrocannabinol (THC), or AP-CBD/THC, for the treatment of various indications, including pain management. The company plans to initiate a phase I clinical trial with AP-CBD/THC during the first quarter of 2017.

Clinical testing by others appears to indicate that extracts of the *Cannabis sativa* plant containing known amounts of the active compounds (mainly THC and CBD) or diverse synthetic derivatives of THC are promising treatments supported by high-quality evidence for painful conditions that do not respond to available treatments, such as chronic, neuropathic, inflammatory, and oncologic pain.

AP-CBD/THC holds potential to address the major drawbacks of current methods of use and treatment with cannabis and cannabinoids such as short duration of effect, delayed onset, variability of exposure, dose variability, narrow therapeutic window, and adverse events that correlate with peak levels.

“We are excited to be expanding our development work to include cannabinoid-based therapies. Current methods of use and treatment with cannabis and cannabinoids are short-acting, which leads to a variety of therapeutic obstacles and gives rise to the need to improve the efficacy and safety of cannabinoids as therapeutics. We believe our Accordion Pill offers a unique opportunity to provide a long-acting oral therapy of cannabinoids for various indications,” said Zeev Weiss, chief executive officer of Intec Pharma. “We believe that utilizing our proprietary platform technology may significantly extend the absorption phase for CBD and THC, thereby resulting in a prolonged and consistent therapeutic effect.”

Intec Pharma Ltd. is a clinical stage biopharmaceutical company focused on developing drugs based on its proprietary Accordion Pill platform technology. The company's Accordion Pill is an oral drug delivery system that is designed to improve the efficacy and safety of existing drugs and drugs in development by utilizing an efficient gastric retention and specific release mechanism. The company's product pipeline currently includes three product candidates in clinical trial stages: Accordion Pill Carbidopa/Levodopa, or AP-CDLD, which is being developed for the indication of treatment of Parkinson's disease symptoms in advanced Parkinson's disease patients, Accordion Pill Zaleplon, or AP-ZP, which is being developed for the indication of treatment of insomnia, including sleep induction and the improvement of sleep maintenance, and an Accordion Pill that is being developed for the prevention and treatment of gastroduodenal and small bowel nonsteroidal anti-inflammatory drug-induced ulcers.

Frost & Sullivan Applauds IFP's Superior Technology Performance and Best Practices in Providing Tailored, Application-Specific Encapsulated Food Ingredients

PRNewswire: August 1, 2016 – MOUNTAIN VIEW, CA, U.S.A. – Based on its recent analysis of the food encapsulation market, Frost & Sullivan recognizes Innovative Food Processors, Inc. (IFP) with the 2016 North America Frost & Sullivan Award for Technology Innovation. IFP's proprietary PrimeCAP® range of encapsulated ingredients offer distinct benefits, such as customization and cost efficiency, to the food and beverage industry. The micro-encapsulated ingredients, supplied as free-flowing powders, are available as both tailored and ready-made products.

In conventional top-down or bottom-up fluid-bed spraying systems, the particles are hit head-on with the coating droplets to form a collision effect, resulting in imperfect coating layers replete with microscopic splashes, gaps, and voids on the particle surface. IFP's patented tangential spray system, on the other hand, has an angular impact on the powder particles of active materials, causing them to rise up and spin through a cloud of coating material. The rotating effect creates longer coating layers over the particle surface, and repeated passage through the coating zone in the fluid-bed results in the formation of multiple layers on the particle surface.

“IFP's adoption of a tangential spray coating system in its fluid-bed processors allows the company to uniquely produce a series of smooth coating layers over the food ingredient particles in a consistent manner,” said Frost & Sullivan Research Analyst Afia Allapitchai. “The fabrication of multiple layers endows the particles with higher resilience against any physical stress, while the thinner coating layers create a longer path for moisture to seep through and reach the core material.”

In addition, manipulating the particle size, coating material used, and number of individual layers of coating materials deposited over the particle surface can alter the controlled interaction properties of the encapsulated food ingredients. This flexibility in manufacturing the encapsulated ingredients allows IFP to apply thinner coating layers. In the past, IFP's encapsulation technologies applied nearly

40% coating on the food ingredients; it now manufactures encapsulated products with as little as 15 to 5% coating, reducing coating usage and operating costs without lowering ingredient performance.

IFP has the largest batch fluid-bed capacity in North America. The PrimeCAP® ingredients are typically manufactured using conventional fluid-bed units that are customized by IFP with sensors and controls for handling encapsulation processes. The equipment optimally processes particle sizes in the range of 50 microns to 5,000 microns in diameter, enabling ingredient use in a wide range of food applications.

The PrimeCAP® encapsulated ingredients are primarily used in the bakery, meat, confection, snack food, and beverage industries for its benefits of controlled release, flavor masking and extension, superior shelf life, and isolation of active materials until interaction is desired. Some of its key encapsulated products include hot-melt coated leavening and mold inhibition ingredients in baking, acidulants for pH control and flavor contribution in meats, and salt for inhibiting interaction with meat proteins and reducing freeze/thaw impact of salt in frozen meats and vegetables.

“IFP also aims to deliver encapsulated ingredients to non-food-based industries that use food-grade raw materials such as the cosmetic and dermatology sectors. The company provides encapsulated citric acid to the petroleum industry as an environment-friendly ingredient to support the fracking process,” noted Allapitchai. “This ability to encapsulate any ingredient that meets the food-grade requirement enables IFP to capture newer markets.”

The company is currently expanding its application laboratory to develop and evaluate new and unique ingredients and applications, specifically in the bakery and beverage industries. Overall, IFP’s capability and strategic initiative to adapt its encapsulation process according to the client’s requirements bestows the company with a significant competitive advantage.

Each year, Frost & Sullivan presents this award to the company that has demonstrated uniqueness in developing and leveraging new technologies that significantly influence both the functionality and the customer value of products and applications. The award lauds the high R&D spend toward innovation, its relevance to the industry, and its impact on brand perception.

IFP develops and delivers high-performance powders that exceed expectations in solubility, taste, and sensory characteristics. We take pride in 35+ years of collaboration and partnership with leading global food, supplement, sports nutrition, direct selling, and medical food companies. We offer customized support, turnkey manufacturing, and expertise in every stage of the powder product development process.

We specialize in functional beverages, sports/nutrition supplements, and medical foods containing high-value ingredients. Customized processing services include leading-edge agglomeration and micro-encapsulation technologies and versatile packaging solutions. NSF registered cGNP for dietary supplements and SQF level III certified. For more information on IFP’s product development and processing, please visit our website: ifpinc.biz. ■