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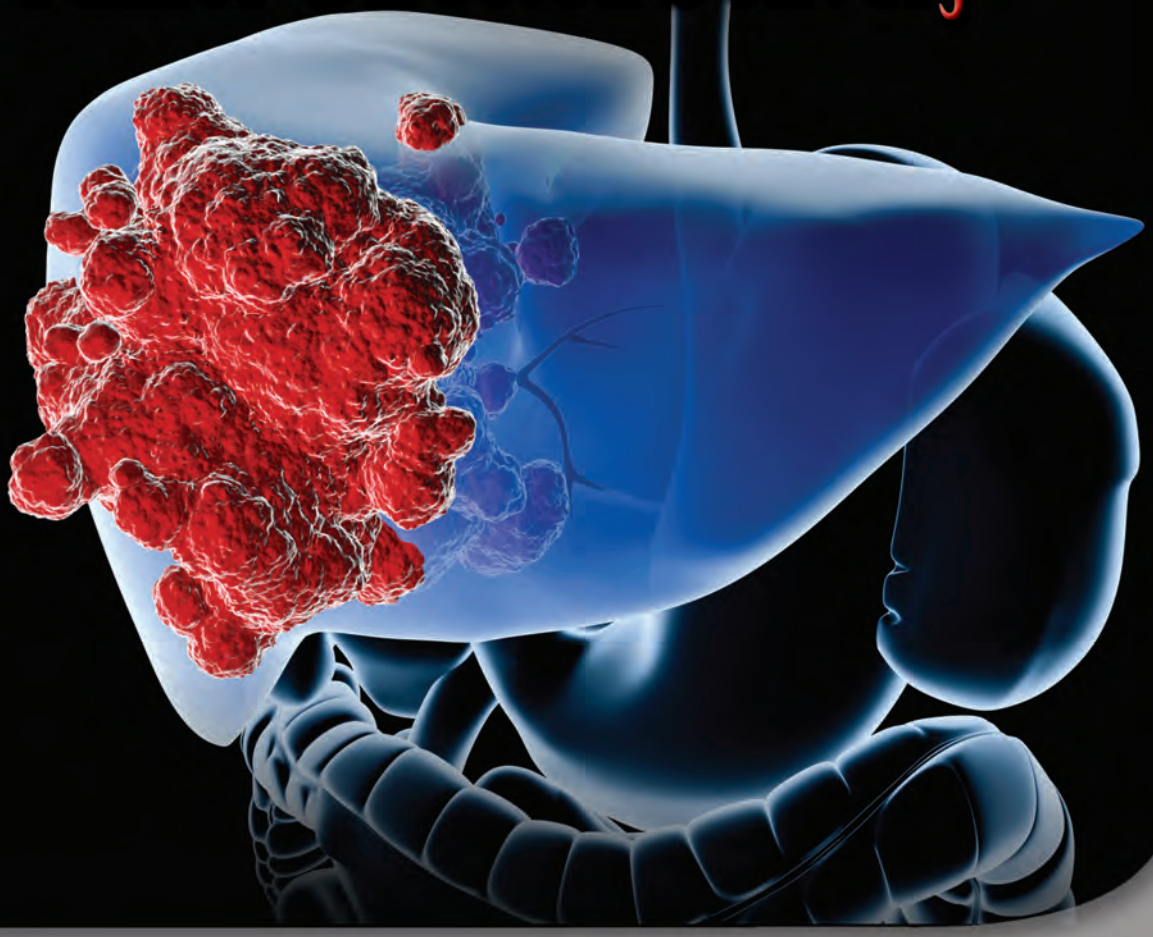
Drug Development & Delivery

April 2016 Vol 16 No 3 www.drug-dev.com

Encore™: Optimizing Tumor-Directed Delivery



The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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EnCore™: Facilitating Delivery of RNAi Therapeutics to Treat Cancer

Franklin Monzon, PhD
One Size Does Not Fit All: Nanoparticle Size Analysis for Nanomedicine Applications

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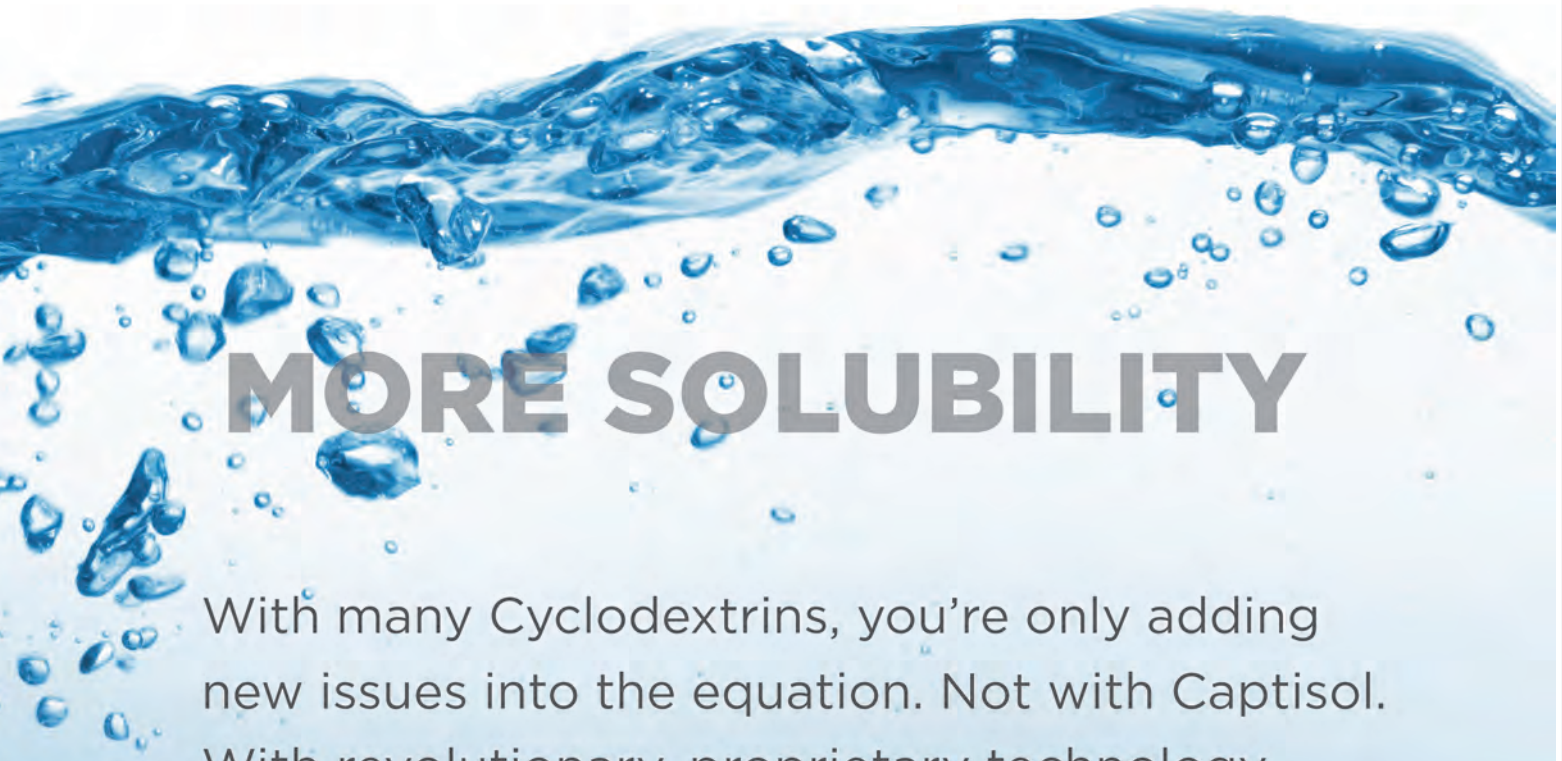

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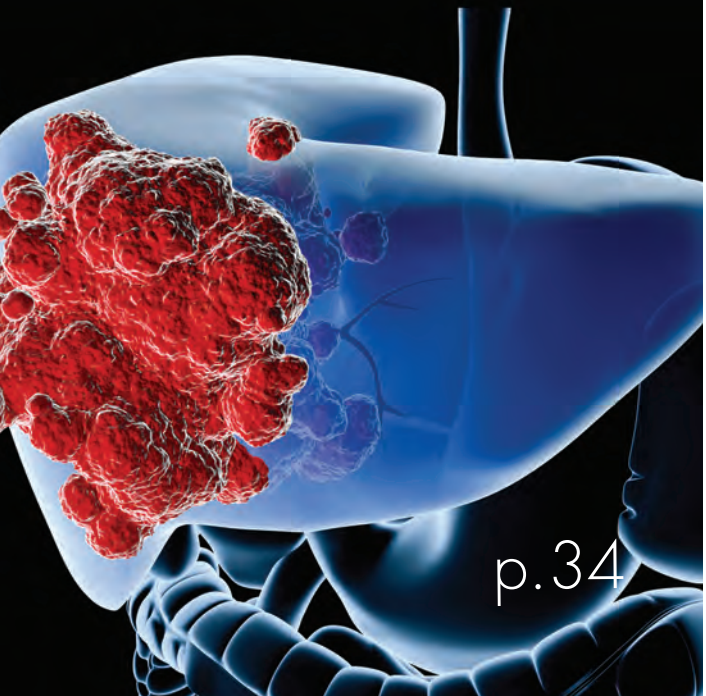

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Outsourcing Development & Manufactruing

"As pharma/biopharma companies look to expand their use of outsourcing in the areas of development and manufacturing, they want to do so with a single provider. Approximately 40% of the survey respondents believe it is very important to use a one-stop-shop CDMO to fulfill their needs from R&D through to commercialization."

p.44

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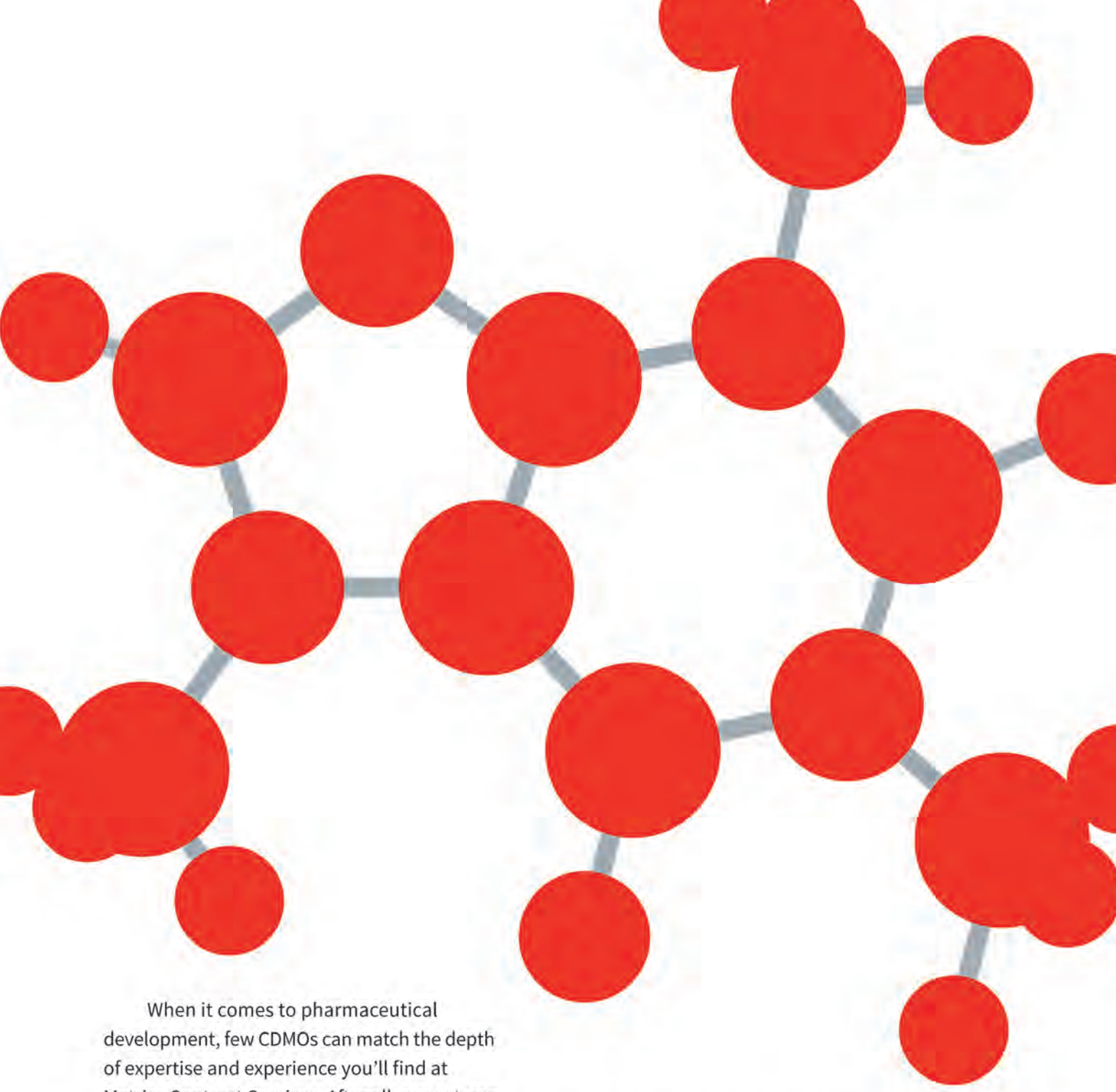

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Daiichi Sankyo & ArQule Announce Continuation of Phase III Study

ArQule, Inc. and Daiichi Sankyo recently announced that the independent data monitoring committee (DMC) of the METIV-HCC study conducted the planned interim assessment, and it was determined the trial will continue to its final analysis.

METIV-HCC is a biomarker-selected, double-blind, placebo-controlled, pivotal Phase III study evaluating tivantinib (2:1) versus best supportive care in previously systemically-treated patients with MET-high, inoperable HCC, with overall survival as the primary endpoint.

The interim analysis was triggered when at least 60% of the target number of events occurred. The final analysis will take place when 100% of the target number of events occurs. The METIV-HCC trial completed patient accrual in December 2015 with more than 300 patients with MET-high HCC enrolled.

Liver cancer is the sixth most common cancer globally with 782,000 new cases in 2012 and is the second most common cause of cancer-related death with 745,000 deaths in 2012. HCC accounts for about 90% of primary liver cancers. Cirrhosis, chronic hepatitis B and C, and smoking are recognized worldwide as factors increasing the risk of HCC.

Tivantinib is an oral MET inhibitor, currently in Phase II and Phase III clinical trials. In healthy adult cells, MET can be present in normal levels to support natural cellular function, but in cancer cells, MET can be inappropriately and continuously activated. When abnormally activated, MET plays multiple roles in aspects of human cancer, including cancer cell growth, survival, angiogenesis, invasion, and metastasis. The activation of certain cell signaling pathways, including MET, has also been associated with the development of resistance to anti-EGFR (epidermal growth factor receptor) antibodies, such as cetuximab and panitumumab.

In clinical trials to date, treatment with tivantinib has been generally well tolerated and has shown clinical activity in a number of tumors studied. Tivantinib has not yet been approved for any indication in any country. In December 2008, ArQule and Daiichi Sankyo signed a licensing, co-development and co-commercialization agreement for tivantinib in the US, Europe, South America and the rest of the world, excluding Japan, China (including Hong Kong), South Korea, and Taiwan.

In November 2015, ArQule exercised its co-commercialization option for tivantinib in the US. A co-commercialization agreement is expected to be finalized in 2016.

ArQule is a biopharmaceutical company engaged in the research and development of targeted therapeutics to treat cancers and rare diseases. Its mission is to discover, develop, and commercialize novel small molecule drugs in areas of high unmet need that will dramatically extend and improve the lives of patients. For more information, visit www.arqule.com.

Caladrius Biosciences Subsidiary Enters Into Global Collaboration & License Agreement

Caladrius Biosciences, Inc. recently announced that, through its subsidiary, PCT, has entered into a global collaboration with Hitachi Chemical Co., Ltd. that includes licensing, development, and equity components. Hitachi Chemical is a global conglomerate with a growing franchise in life sciences, including regenerative medicine.

As part of the collaboration, Hitachi Chemical has purchased a 19.9% equity interest in PCT for $19.4 million. Caladrius will retain the remaining 80.1% ownership of PCT. Caladrius intends to use the acquired capital for continued expansion and improvements at PCT in support of commercial product launch readiness as well as for general corporate purposes.

In addition, PCT has licensed its cell therapy technology and know-how to Hitachi Chemical for cell therapy manufacturing in certain Asian territories, including Japan, where the Pharmaceuticals and Medical Devices Agency (PMDA) has introduced more favorable legislation to stimulate the growth of regenerative medicine development. Under the license agreement, Hitachi Chemical is to make upfront and near term milestone payments of $5.6 million. In addition, Hitachi Chemical will pay service fees and royalties on contract revenue in those territories. Under the license arrangement, Hitachi Chemical is responsible for all capital and operational expenses associated with the establishment and operation of the Asian business on which PCT is entitled to royalty payments.

PCT and Hitachi Chemical have also agreed to explore the establishment of a joint venture in Europe.

"We are delighted about this collaboration with a company of the stature and global reach of Hitachi Chemical as it represents a clear validation of the PCT business model, technology, and know-how. Importantly, it now values our PCT business at approximately $100 million and provides non-dilutive capital that strengthens our financial position," said David J. Mazzo, PhD, Chief Executive Officer of Caladrius. "Together, Caladrius, PCT and Hitachi Chemical are focused on building a global leadership position in cell therapy development and manufacturing with this transformative collaboration."

"This partnership with Hitachi Chemical underscores the value of PCT's expertise in cell therapy manufacturing and process development and will allow for the acceleration of our vision to create a global commercial enterprise with deep engineering expertise. Moreover, Hitachi Chemical's investment in PCT shows its confidence in the growth of the cell therapy field as the field continues to shift towards Phase II and Phase III trials and into commercial distribution as regulatory approvals are obtained," said Robert A. Preti, PhD, President of PCT. "By leveraging this expanded footprint, our clients will gain global access to the cell and cell-based gene therapy markets of tomorrow, where we expect engineering solutions to process optimization and automation will play a seminal role."

"Our aim is to establish global leadership in regenerative medicine, and we believe this deep collaboration with PCT, through its veteran cell therapy manufacturing experts and global brand, can power that into a reality," added Kazuyuki Tanaka, President and CEO of Hitachi Chemical Co., Ltd. "By leveraging PCT's expertise and cell therapy technology, complementing PCT's capabilities with our own and launching joint initiatives in new geographies, we will advance together towards that goal. In addition to using PCT's support, Hitachi Chemical will receive technological assistance from Hitachi Group to develop a production control system, including automated facilities, to manufacture low-cost yet high-quality regenerative medicine cells, while also promoting consumable materials such as containers and reagents."

Topi-CLICK Revealed as Most Accurate Topical Metered-Dosing Dispenser in Independent Study

Since introducing Topi-CLICK in 2007, DoseLogix has emphasized superior accuracy and precision compared to other topical metered-dosing dispensers. Now there is scientific research to confirm it.

In a recent study of five topical metered-dosing dispensers on the market, conducted by Analytical Research Laboratories in Oklahoma City, OK, Topi-CLICK earned top marks. "Overall, the study shows Topi-CLICK performed with remarkable precision and accuracy compared to the other dispensers," the report concluded.

The study was designed to evaluate, "the accuracy, precision, and residual of current topical metered-dosing dispensers using three different types of topical creams for practical application." The test featured five brands of dispensers filled with three commercial cream-bases of dissimilar Total API Load Percentages, Transdermal Penetration Percentages, and Specific Gravities. In each case, Topi-CLICK showed superior precision and consistency in comparison to the airless-pump dispensers.

"Most remarkably, Topi-CLICK performance did not vary from one cream-base type to the next," the study reports. "Therefore, Topi-CLICK was not affected by the various types of cream-bases used in this study, and seemed to be easier to use."

DoseLogix's innovative, user-friendly Topi-CLICK has become the applicator-of-choice for an ever-increasing list of pharmacists, doctors, and patient advocates. "This detailed study was able to scientifically show what many consumers and healthcare professionals have known all along," said DoseLogix CEO Tim Phipps. "Topi-CLICK is the most accurate and consistent topical-dosing dispenser on the market based on the results of this recent study. We take pride in maintaining the highest standards."

DoseLogix, based in Atlanta, GA, manufactures a variety of products to support its flagship brand, Topi-CLICK, including the Topi-CLICK 35, the larger volume Topi-CLICK 140, and the revolutionary Perl Vaginal Dosing Kit. Since launching the revolutionary topical applicator Topi-CLICK in 2007, DoseLogix has continued to be a pacesetter in the healthcare industry. In its ongoing effort to make it easier for patients with a wide variety of needs to obtain an accurate dose, DoseLogix has been unrelenting in pursuing new technologies and innovation. Patients, doctors and compounding pharmacists have shown their appreciation with enthusiastic, word-of-mouth endorsements. For further information on ITS products, please visit www.DoseLogix.com, call (800) 870-8448, or email info@DoseLogix.com. To request a copy of the independent study, visit www.doselogix.com/accuracy_study/.

Genisphere Enters Collaborative Nanotherapeutics Research Agreement

Genisphere LLC has signed a collaborative research agreement with the University of Pennsylvania to study targeted nanotherapeutics in cancer treatment. The collaboration between Genisphere LLC, provider of the 3DNA drug delivery platform, and the University of Pennsylvania, through Dr. Theresa Busch, will utilize a breast cancer model to study photodynamic therapy (PDT).

PDT is a complementary treatment option that can be added to surgery for removal of residual cancer. Photosensitizing drugs are administered to patients prior to surgery, and then activated by visible light after the tumor tissue is removed, to destroy cancerous cells left behind. The delivery of PDT to the entire surgical field is essential, thus selective photosensitizer accumulation in diseased cells is necessary to avoid therapy-limiting damage to normal tissues.

"When used in the intraoperative setting, PDT provides for local treatment at the site of surgery and can be effective in eradicating undetected or unresectable tumor," said Dr. Theresa Busch. "This concept is suggested by patient outcomes in our previous clinical trials of intraoperative PDT for malignant pleural mesothelioma, and we are currently conducting a randomized Phase II clinical trial for this indication. This approach can be adapted for intraoperative PDT of breast cancer; however, the addition of a photosensitizer that is targeted to breast cancer cells could broaden the therapeutic window and selectively increase cytotoxic effect."

Physician collaborators in the Department of Radiation Oncology, Drs. Keith Cengel and Gary Freedman, respective chiefs of the clinical PDT and breast cancer services, indicated photosensitizer targeting for breast cancer PDT would fuel its clinical translation.

"We hypothesize targeted 3DNA will increase tumor uptake of photosensitizer relative to surrounding mammary tissue, providing for greater efficacy and minimal toxicity in the delivery of PDT."

Tom Bliss, Genisphere's Chief Executive Officer, added "This is the perfect partnering opportunity for Genisphere because of its immediate clinical relevance. It is our earnest desire, in establishing this agreement with Penn, to create the standard for many to come."

Genisphere LLC is the provider of the 3DNA platform for targeted drug delivery. 3DNA is a nanoscale, multivalent scaffold made from proprietary, synthetic DNA formed in a flexible, branched structure. 3DNA nanocarriers are engineered and cross-linked to form a stable architecture while maintaining the biocompatibility of the nucleic-acid building blocks, and demonstrate efficacy and safety with a variety of drug cargos across multiple indications. Genisphere's technology is IP-protected and fully customizable to deliver small molecules, biologics, and nucleic acids with precise specificity enabled by multivalent targeting via antibodies, peptides, and other molecular entities. Genisphere leverages a collaborative model to advance its 3DNA drug delivery platform, and seeks additional partnerships with biotechnology and pharmaceutical companies to improve efficacy and reduce toxicity. Genisphere is also advancing its own lead compounds based on 3DNA nanotechnology. For more information, visit www.genisphere.com.

NDA Group & PharmApprove Announce Merger

NDA Group and PharmApprove recently announced their merger. The newly combined company will allow clients to streamline the global development and commercialization process, accelerating patient access to important medical therapies. Through the merger, NDA and PharmApprove will offer clients an unparalleled breadth of global experience and expertise to drive efficient product development across the US and Europe.

"NDA has supported over 45% of new medicinal products that were approved in Europe over the past 3 years, and more than half from the past year," said Johan Strömquist, CEO of NDA Group. "By working together, NDA and PharmApprove offer clients a single partner that can provide a clear development path – considering both regulatory and market access requirements – to offer streamlined, strategic drug development advice across the world's two largest markets."

"With a high success rate of supporting clients preparing for FDA Advisory Committees and other regulatory milestones, PharmApprove has a long track record of great results," added Laurie Smaldone Alsup MD, President of PharmApprove. "We will continue to provide comprehensive advisory committee services and expand our global support. Our culture is a perfect complement to NDA Group; we both believe in engaging highly experienced and high-quality people who provide expert guidance to our clients."

The combined companies offer more than 35 years of experience in the drug development space, and boast a network of over 1,000 experts across a range of technologies, disciplines, and therapeutic areas. NDA and PharmApprove will each retain their current staff and leadership, including more than 150 consultants, while adding to their capabilities and transatlantic reach.

"The deep knowledge of regulatory agencies and their requirements that I and my fellow NDA and PharmApprove consultants can provide is essential for any company looking to bring important new treatments to patients in need," said NDA Group's Strategic Advisor, and former head of the European Medicines Agency, Dr. Thomas Lönngren. "With our involvement in every step of the drug development process, we can prevent costly missteps – and ultimately ensure that clients have the best chance to prove the safety and efficacy of their drugs worldwide."

"My experience working with NDA and PharmApprove clearly demonstrated that this is a case where the whole is greater than the sum of its parts," explained Dr. Ron Robison, Vice President, Global Regulatory Affairs, Pharmacovigilance and R&D QA for AbbVie. "Having seamless, simultaneous access to regulatory experts in multiple markets helped us to develop the strategies we need to support optimal labeling and market access opportunities."

Aduro Biotech Announces First Patient Dosed in Combination Clinical Trial

Aduro Biotech, Inc. recently announced that the first patient has been dosed in SEASCAPE, the Phase I/II clinical study designed to evaluate the safety, tolerability and preliminary efficacy of CRS-207, Aduro's lead listeria-based immunotherapy construct (LADD), in combination with epacadostat (INCB24360), Incyte Corporation's selective IDO1 inhibitor, in patients with ovarian cancer.

"By combining two immuno-oncology therapies, which we believe have synergistic mechanisms of action, we and Incyte look forward to potentially advancing new treatment options for patients with ovarian cancer that could result in more effective therapy than either therapy alone," said Stephen T. Isaacs, Chairman, President and Chief Executive Officer of Aduro. "Combination therapy is rapidly emerging as a new paradigm for immuno-oncology. With our three diverse technology platforms – LADD (listeria-based therapy), STING pathway activators and monoclonal antibodies – we intend to continue to identify new opportunities to improve patient care."

SEASCAPE (Study of Epacadostat and CRS-207 in Adults with Platinum Resistant Ovarian Cancer), co-funded by Incyte and Aduro, is designed to establish a recommended dose based on safety and tumor biomarkers for CRS-207 and epacadostat in Phase I followed by expansion into Phase II, which will evaluate the combination at the recommended (or identified) dose level compared to CRS-207 alone. Aduro plans to enroll up to 40 patients in Phase I and up to 86 patients in Phase II with platinum-resistant ovarian, fallopian, or peritoneal cancers.

Aduro and Incyte will collaborate on a non-exclusive basis. Aduro will be responsible for conducting the study and the results will be used to determine whether further clinical development of this combination is warranted. Costs for the trial will be shared on an equal basis.

Indoleamine 2,3-dioxygenase 1 (IDO1) is an immunosuppressive enzyme that has been shown to induce regulatory T cell generation and activation, and allow tumors to escape immune surveillance. Epacadostat is an orally bioavailable small molecule inhibitor of IDO1 that has nanomolar potency in both biochemical and cellular assays and has demonstrated potent activity in enhancing T lymphocyte, dendritic cell and natural killer cell responses in vitro, with a high degree of selectivity.

Epacadostat has shown proof-of-concept clinical data in patients with unresectable or metastatic melanoma in combination with the CTLA-4 inhibitor ipilimumab, and is currently in four proof-of-concept clinical trials with PD-1 and PD-L1 immune checkpoint inhibitors in a variety of cancer histologies. A Phase III study evaluating the combination of epacadostat with pembrolizumab as first-line treatment for patients with advanced or metastatic melanoma is expected to begin in the first half of 2016.

CRS-207 is one of a family of product candidates based on Aduro's live, attenuated, double-deleted (LADD) Listeria monocytogenes immunotherapy platform that induces a potent innate and T cell-mediated adaptive immune response. CRS-207 has been engineered to express the tumor-associated antigen mesothelin, which is over-expressed in many cancers including mesothelioma and pancreatic, non-small cell lung, ovarian, endometrial and gastric cancers.

Placon Therapeutics Announces Company Launch and FDA Acceptance of IND

Placon Therapeutics recently announced its launch as an independent company and provided an update on its lead product candidate, BTP-114, for which the US FDA has accepted an Investigational New Drug (IND) application to begin clinical evaluation in cancer patients. Placon was spun out from Blend Therapeutics, Inc. (now Tarveda Therapeutics, Inc.) to distinctly focus on a pipeline of innovative platinum-based assets.

Placon plans to pursue the development of novel platinum-based cancer therapies that are designed to substantially improve the efficacy and side effect profile of widely used traditional platinum medicines. Specifically, Placon is focused on advancing BTP-114 into clinical studies in patients with refractory solid tumors, and the company is seeking to advance this lead candidate into clinical development through collaboration with a strategic partner or with investors.

"Platinum-based drugs are a cornerstone of many therapeutic regimens for patients with solid tumors, and we believe that BTP-114 reflects the latest innovations in cancer R&D to offer improvements beyond today's cytotoxic medicines that may provide enhanced benefits for cancer patients," said M. James Barrett, PhD, a Director of Placon Therapeutics and investor at New Enterprise Associates (NEA). "The FDA's acceptance of the clinical trial approach for BTP-114 is an important milestone in the development of this promising cancer drug candidate, and we are actively seeking collaborative opportunities to move forward into the clinic."

In April 2015, preclinical data for BTP-114 were presented at the American Association for Cancer Research (AACR) Annual Meeting. These studies demonstrated sustained tumor growth inhibition in multiple xenograft models and reduced dose-limiting toxicities compared to cisplatin. The presentation also described the mechanism of Placon's advanced platinum drugs, which take advantage of emerging insights from cancer biology, genomics, and molecular tumor targeting. Once administered, BTP-114 conjugated with serum albumin to allow long circulating half-life before preferential uptake by cancer cells with certain molecular profiles, showing results in the study of a 13-fold increased accumulation of platinum in the tumor.

BTP-114 is the first clinical candidate discovered using Placon's novel albumin-conjugating, platinum-prodrug platform developed by its industry leading chemistry and biology teams and built on the pioneering work of the company's scientific co-founder, Professor Stephen J. Lippard of the Massachusetts Institute of Technology, who is a world leader in platinum chemistry.

Placon Therapeutics is a biotechnology company developing next-generation novel platinum medicines designed to improve the efficacy and side effect profile of today's cytotoxic medicines that are widely used in cancer treatment. For more information, visit www.placontx.com.

Ajinomoto Althea Expands Capacity of Fill Finish Manufacturing

Ajinomoto Althea, Inc. recently announced it is expanding the capacity of its Fill and Finish operations through the addition of a second manufacturing shift. Althea's contract manufacturing business has experienced exceptionally strong growth driven by biotech companies outsourcing to Althea sterile fill and finish parenteral manufacturing to support their clinical and commercial drug programs. In 2015, Althea's business grew by 30%, and it expects to continue on this steep growth trajectory in upcoming years. Althea's second shift will come on-line in early June, increasing the number of manufacturing slots for commercial and clinical drug programs, thereby significantly reducing lead times from project kickoff to fill date.

"We are very pleased and eager to provide this additional fill and finish capacity to all of our clients. We recognize and appreciate the need for shorter lead times and flexible timelines, which are critical to developers of biologics-based drug products. The addition of this second manufacturing shift will allow us to further accommodate the substantial increase in demand we've observed from our clinical and commercial partners," said Chris Duffy, Senior Vice President of Operations.

To support this significant increase in its parenteral manufacturing capacity, Althea has invested in additional operational capabilities, more visual inspection suites, automated quality systems, and project management expansion. This expansion plan is one element of the growth strategies that Althea is deploying to accommodate not only the increased demand in its fill and finish business, but also in its microbial and plasmid DNA capabilities, its proprietary crystallization formulation technology (Crystalomics) programs, and its recently announced entry into the highly potent API and ADC bioconjugation and fill and finish services.

Althea is a fully integrated, contract development and manufacturing organization located in San Diego, CA, providing clinical and commercial product development services. Althea offers cGMP drug product filling in both vials and syringes, and production of microbial-derived recombinant proteins and plasmid DNA. In conjunction with these manufacturing operations, Althea offers comprehensive development services, including upstream and downstream process development, analytical development, complex formulation, product release and ICH-compliant stability testing. Althea's formulation technology platform includes Crystalomics, a proprietary technology that offers a formulation solution for large molecule products that must be delivered at high concentrations or as sustained release formulations. Althea also has an innovative and proven recombinant protein expression technology called Corynex technology. For more information, visit www.altheaCMO.com.

NANOPARTICLE CHARACTERIZATION

One Size Does Not Fit All: Nanoparticle Size Analysis for Nanomedicine Applications

By: Andrew N. Cleland, PhD, Jean-Luc Fraikin, PhD, Peter Meinhold, PhD, and Franklin Monzon, PhD

ABSTRACT

The use of nanoparticles for drug delivery is receiving increasing attention by researchers in academia, industry, and federal research institutions. Monitoring the size distribution of nanoparticles is an important requirement for process control, for evaluating the efficacy of the drug delivery strategy, and for ascertaining the potential for dangerous, possibly fatal, immunogenic responses in patients treated with nanoparticle-based drugs. Here, we describe a new diagnostic instrument able to rapidly and accurately report detailed nanoparticle size distributions for a wide variety of nanoparticle types and concentrations in a range of different solutions.

INTRODUCTION

Nanoparticle-based drug delivery systems are of great interest to drug developers in industry and academia, primarily because they provide an alternative means for targeting and delivering therapeutic treatments to patients. These systems offer a number of potential advantages, including better stability, reduced side-effects, and the ability to target the delivery of a wide range of drugs and other therapeutics.[1] In addition, there has been significant interest in using nanoparticles as vehicles for vaccine delivery.[2,3] However, such nanoparticle-based systems can trigger adverse immune responses, driven by such variables as nanoparticle size and the detailed surface properties of the nanoparticles.[4] Furthermore, unintended processes, such as aggregation or modification of the surface composition of nanoparticles in a formulation, may interfere with the effectiveness of the delivery or action of the drugs, and possibly cause harm in patients treated with the faulty products.

Unfortunately, instrumentation that can quickly and accurately report the size distribution of nanoparticles, and monitor the evolution of these distributions, has until now been essentially unavailable. This is especially acute for nanoparticles below roughly 1 micron in diameter. Dynamic light scattering (DLS) is a highly popular tool in this area, mostly due to its ease of use and its ability to detect a very wide range of particle sizes. However, DLS is well known to suffer from severe limitations, most prominently stemming from its inability to accurately measure polydisperse solutions: in samples with mixed particle populations, DLS often reports a single peak in a particle distribution when in fact there are a number of distinct groups of particle diameters. Reliable measurements of smooth distributions spread over a few diametric octaves are also highly problematic. Furthermore, DLS is unable to provide any concentration information, even though this is often a critical parameter in monitoring or debugging a nanoparticle production process.

Some of the challenges faced by DLS are being circumvented by emerging light-scattering technologies that track and size individual particles. However, these technologies share with DLS the fundamental challenge that particles with an optical index close to that of the suspension medium scatter much less light than those with a significantly different index.

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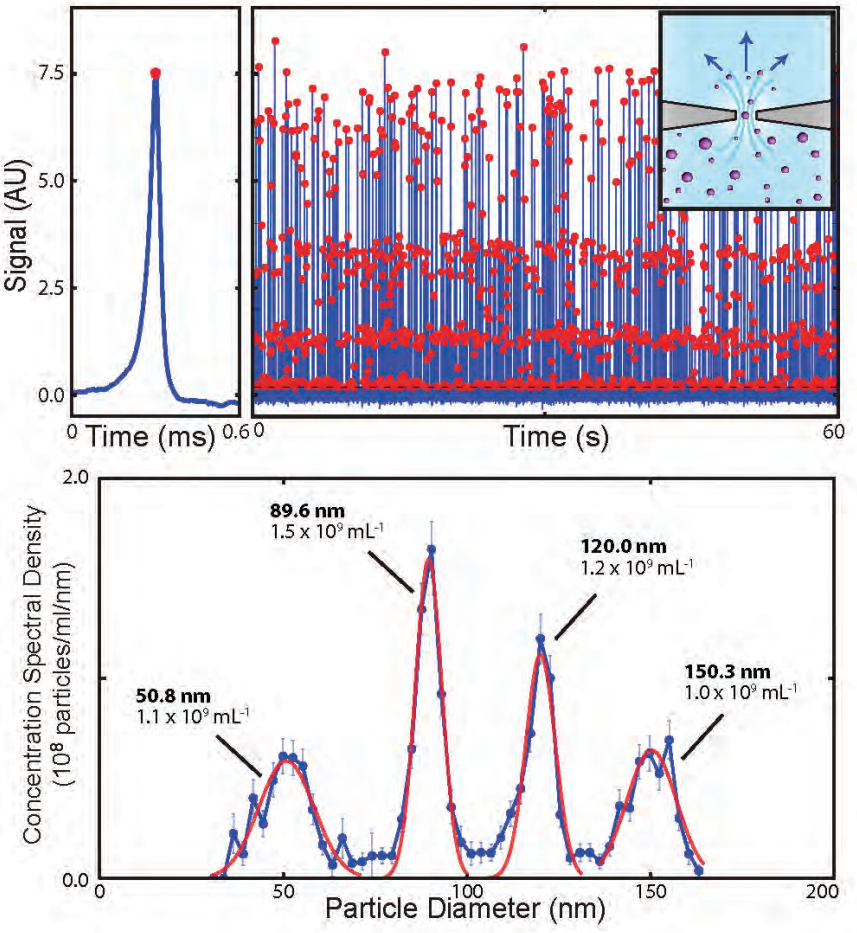
This sensitivity dependence makes some types of particles essentially undetectable, and creates a bias toward "brighter" particles. As a result, light-based particle tracking provides a limited ability to measure a variety of biologically relevant particles with diameters less than 100 to 200 nm, despite the fact that the "sweet spot" for drug delivery applications is thought to be below this size range. Other limitations include a quite restricted range of measurable concentrations, and a requirement that the data analysis software reliably distinguish and accurately track particles, a requirement that is difficult to validate.

CONCENTRATION SPECTRAL DENSITY™

Spectradyne LLC has recently released a novel nanoparticle characterization instrument, the nCS1, which is capable of measuring the size distribution of nanoparticles with diameters ranging from 30 nm up to a few microns, over a wide range of nanoparticle concentrations, from 10^7 to 10^{12} particles/ml. The instrument can report accurate size distributions of a wide variety of nanoparticles in a range of suspension media, and reports the data in absolute nanoparticle concentration units.

The basis for this new instrument is the well-established resistive pulse sensing technique, implemented by Spectradyne in a miniaturized and disposable microfluidic cartridge. The basic concept involves passing a weakly conducting analyte carrying the nanoparticles or microparticles of interest through a small constriction having a diameter of a few hundred nanometers to a few microns (Figure 1). A bias voltage is applied across the constriction, and the electrical resistance of the current path through the analyte and the constriction is monitored. When a nanoparticle passes through the constriction, it blocks some of the electrical sensing current, increasing the electrical resistance of the constriction by an amount proportional to the nanoparticle volume. Monitoring the electrical resistance as a function of time thus yields a number of short pulses, each corresponding to the passage of one nanoparticle, with the pulse amplitude yielding the nanoparticle

FIGURE 1



Top left: Detection events are resistance pulses in time, where the amplitude is proportional to particle volume, and the duration of the pulse is inversely proportional to the suspending fluid velocity. Right: Data acquired over 60 seconds, where each red dot corresponds to one particle's fit pulse height. The distribution of red dots along the vertical axis corresponds to the distribution of particle volumes in the sample. Concentration information is obtained from the flow rate, calculated from the average pulse width. Inset: Schematic of the resistive pulse sensing technique, in which nanoparticles pass through a nanoconstriction, blocking the flow of electrical current and increasing the electrical resistance through the nanoconstriction. Bottom: Analysis of the time-based data results in a concentration spectral density (CSD), where the vertical axis gives the number of particles per ml per nm of diameter, as a function of particle diameter. Red curves are fits to the distributions. Integrating the blue data over the fit range gives the concentrations listed under each mean diameter, where the concentrations are reported as number of particles per ml.

FIGURE 2

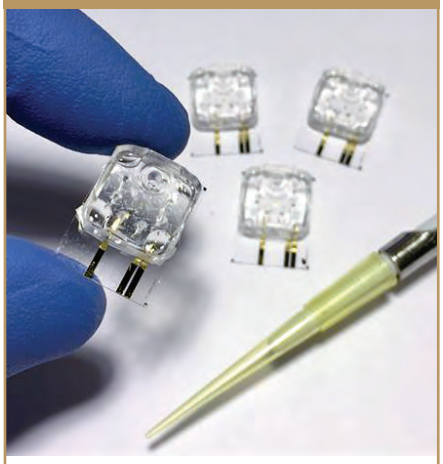


Image of the disposable microfluidic cartridge, the heart of the Spectradyne nCS1 instrument.

volume, and the duration corresponding to the particle dwell time, and thus the particle velocity. As the particles are entrained in the suspending fluid, the pulse duration yields the volumetric flow rate. One can thus obtain the concentration of nanoparticles as a function of nanoparticle size, directly from the time trace of the electrical resistance. For the instrument to work properly, the aqueous solution must have a conductivity that falls roughly in the range of 0.1 to 1 S/m, typically achieved by dissolving 0.01 to 1 M of salt in water. Phosphate-buffered saline (PBS), for example, serves well, and blood serum and urine have the appropriate levels of conductivity.

In Spectradyne's implementation of the resistive pulse sensing technique, particles are detected in a disposable microfluidic cartridge that forms the core of the nCS1 (Figure 2). The sample to be analyzed is pipetted into a reservoir in the cartridge (just 3 microliters of analyte are required), and the cartridge is loaded into the instrument for measurement. The analyte is prevented from contacting any other instrument components prior to analysis, removing any possibility of cross-contamination. After engaging the cartridge with the instrument, automated software controls the microfluidics and data acquisition, and complete data sets can be generated within a minute or so.

Following data acquisition, software-based analysis of the data produces the basic output of the instrument, which comprise particle histograms as a function of particle size. The particle concentration is reported in the form of a concentration spectral density (CSD™), which corresponds to the number of particles per ml of analyte solution per nm of particle diameter, with an example shown in Figure 1. The absolute concentration of particles in a range of particle diameters can be calculated using a software integration tool, generating size histograms with user-defined diametric bin widths, where the number of particles per ml is provided for each size bin. Examples of similar integrated concentrations are given in Figure 1. The use of the CSD allows inter-comparing measurement results from different samples using different cartridges, as the CSD is independent of the cartridge parameters as well as the widths of the bins used to report particle concentrations.

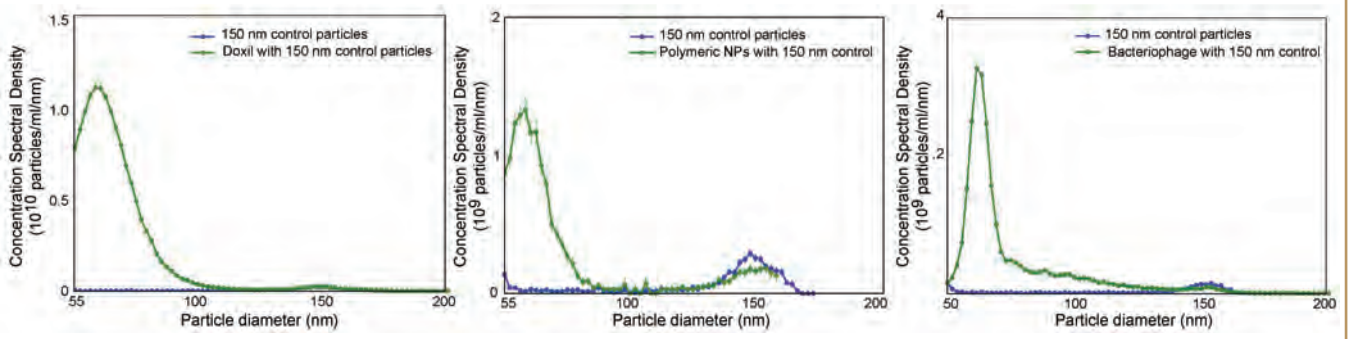
The resistive pulse sensing technique, which is also known as the Coulter principle[5,6] and forms the basis for hematologic whole cell counting, works regardless of whether the nanoparticles are made of an insulating or conducting material: a given diameter polystyrene or colloidal particle will give the same signal as the same diameter gold or other metal particle. This is because electrochemical barriers to electrical conduction through even a good metallic conductor are far too large for the nature of the particle to make a difference.

HIGHLY-ENGINEERED ANALYSIS CARTRIDGES

An image of the disposable analysis cartridge is shown in Figure 2. While containing nanoscale features, the cartridges are produced at low cost using standard molding techniques, allowing the inexpensive reproduction of nanoscale features via casting from a master mold. Using NIST-traceable standard particles, Spectradyne has shown that diametric measurements on nanoparticle samples are reproduced to within 1% to 2%, using different cartridges cast from the same mold. The detailed design of the cartridge, and the methods used for reproducing it from a master mold, follow closely the principles in a recent publication,[7] in addition to the accompanying patent.[8]

The disposable microfluidic cartridge affords a number of powerful advantages over other competing techniques. First and foremost, the maximum sample volume used in an analysis is only 3 microliters, set by the size of the analyte reservoir in the disposable cartridge. This is highly appealing for situations in which the test formulation is expensive or difficult to produce, and provides a significant and welcome reduction in volume from what is needed in, eg, DLS-based analyses. Secondly, the very high count rates afforded by Spectradyne's instrumentation means that statistically significant data sets can be acquired in just a few tens of seconds of data

FIGURE 3



High resolution analysis of three nanoparticle formulations composed of different materials. Left: Doxil, a liposomal nanoparticle (mean diameter 64 nm, dispersion 27%, stock concentration 4.5 X 10^{13}/ml; measured sample was diluted 1:130 in suspending buffer). Center: A formulation of polymeric nanoparticles currently in Phase II clinical trials (mean diameter 62 nm, dispersion 21%, stock concentration 4.2 X 10^{13}/ml, diluted 1:1500). Right: A commercial preparation of bacteriophage, showing a broad secondary distribution of larger particles (mean diameter 58 nm, dispersion 11%, stock concentration 1.8 X 10^{11}/ml, diluted 1:1.5). In all cases, NIST-traceable 150-nm diameter polystyrene particles were added to the sample to provide an in situ positive control for the measurement. Measured particle sizes were in agreement with manufacturer's estimates based on results from orthogonal, time- and energy-intensive measurement techniques (eg, TEM).

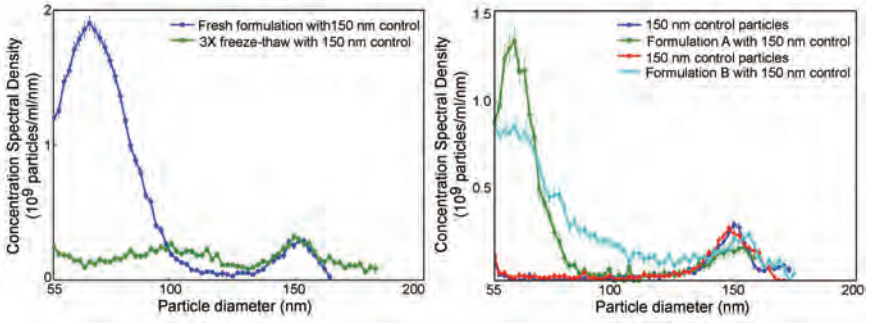
acquisition. Thirdly, the wide range of concentrations that can be reliably measured, from 10^{7} to 10^{12} particles per ml, means that many formulations can be measured as is, often without the potentially problematic need for dilution or concentration. Finally, the low cost of the disposable microfluidic technology means that tests can be repeated multiple times without incurring significant expense, allowing the close observation of an on-going process, or monitoring the stability of a formulation following production.

KEY IMPACT AREAS FOR DRUG DEVELOPMENT & DELIVERY

Formulation Analysis

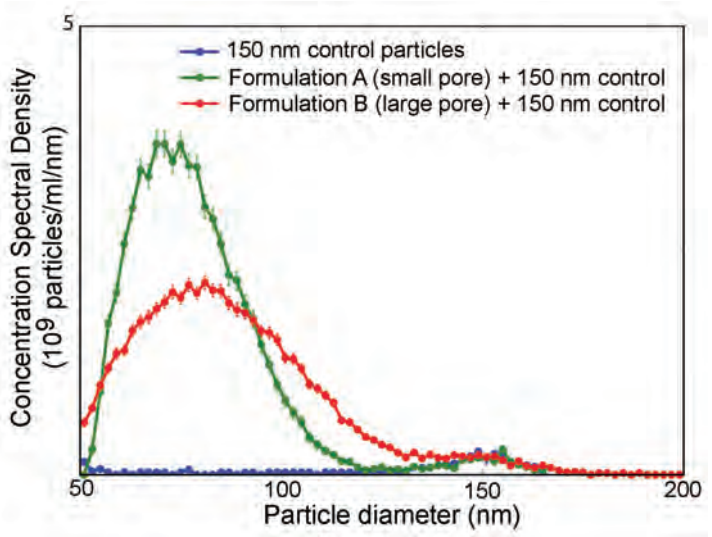
The Spectradyne nCS1 has been used to characterize a wide variety of formulations and biological materials used in the drug delivery industry. High resolution size and concentration distributions for three different examples are shown in Figure 3, including measurements of Doxil, the first FDA-approved nanoparticle-carrier drug formulation; a proprietary polymeric nanoparticle formulation currently in Phase II clinical trials for targeting anti-cancer drugs to tumors; and a commercial bacteriophage preparation used to evaluate sterilization effectiveness in a cell culture manufacturing process. In each case, the sample was combined with a solution of 150-nm diameter NIST-traceable control beads to provide an in situ positive control, and the mixture was diluted in PBS. The nCS1 has also been used to perform high-resolution measurements on polystyrene beads ranging in size from 50 nm to 1 micron; on gold beads in the 50 to 200 nm range; and on biologically derived exosomes, which

FIGURE 4



Formulation stability testing. Left: Effect of three freeze/thaw cycles on a lipid emulsion-based formulation. Before (blue): mean diameter 69 nm, dispersion 30%; after (green): mean diameter 99 nm, dispersion 31%. An increase in the concentration of larger particles (> 150 nm) was also observed (data not shown). Right: Time-dependent degradation of a biocomposite nanoparticle formulation. Before (green): mean diameter 62 nm, dispersion 21%. After (light blue): broad distribution of particle sizes with no clear peak.

FIGURE 5



Effect of extrusion pore size on the concentration-size distribution of particles in a liposomal nanoparticle formulation used for drug delivery. A larger pore size was used to manufacture formulation A (green) compared to formulation B (red), which displays only a slightly larger peak diameter but a much broader distribution. The larger particles in formulation B confound DLS measurements, which instead report an excessively large and misleading difference in mean diameter between the two formulations.

typically have a broad distribution in size from a few tens of nanometers up to a few hundred nanometers, sufficiently broad that DLS cannot properly characterize the population distribution.

Spectradyne's nCS1 delivers two fundamentally new metrics that can be used to characterize a nanoparticle formulation more precisely and effectively. First, the instrument reports absolute particle concentration, a parameter that relates to the bioavailability of a drug and directly informs about the production process. Second, the instrument generates high-resolution, statistically significant measurements of particle size distributions, enabling the accurate characterization of size distribution in a particle population and the detection of spurious particles in nearby size ranges.

Stability Testing

The nCS1's ability to provide high-resolution size and concentration measurements makes the instrument ideally suited for establishing the stability of formulations under different conditions. In Figure 4, we show two examples of this type of analysis: the direct measurement of the effect of freeze-thaw cycling on a lipid emulsion-based drug product, and the detection of the degradation over time of biocomposite particles in a cancer therapeutic formulation. In both cases, there are clear trends brought out by the detailed representation of the data, with aspects frequently undetectable using other means.

Process Characterization

In addition to the storage and handling conditions previously described, different manufacturing methods and processing parameters may have significant effects on the physical characteristics of a nanoparticle product. A complete understanding of the impact of these variables on the quality of the particles is critical at all stages of development and production.

In Figure 5, for example, we show measurements of a liposomal formulation that was manufactured using two different extrusion pore sizes. Spectradyne's nCS1 reveals striking details about the samples, where formulation A, fabricated by extrusion through a small pore, contains a relatively monodisperse particle population centered at 74 nm diameter, with a 1-sigma spread of 28% about the peak and a concentration at stock of 2.9 X 10^{14}/ml. The nCS1 measurement of formulation B, made with a somewhat larger extrusion pore, reveals that there is only a slight change in the peak particle diameter, from 74 nm to 81 nm, and that the concentration of particles in this population falls by roughly a factor of two (to 1.6 X 10^{14}/ml at stock concentration). The nCS1 further detects a significant increase in the dispersion of particle diameters in formulation B using the larger extrusion pore size, from 28% to 39%.

Dynamic light-scattering measurements of these samples, by contrast, report a significant difference in average particle diameter, with 80 nm for formulation A changing to 120 nm for formulation B. The reason DLS makes this rather significant error in the mean particle size for formulation B is that the

larger particles at the tail of the distribution scatter light much more strongly than the smaller particles (scattering intensity in DLS scales as diameter to the sixth power). As a result, the small number of large particles in the distribution tail disproportionately dominates the DLS measurement and confounds the result, leading DLS to report a much larger average particle size than is actually present. Note further that DLS does not report the spread in the particle population about these (misleading) average diameters, and of course does not provide the concentration.

The measurements using the nCS1 clearly indicate that the larger pore used in the production process of formulation B compared to formulation A results in an increase in polydispersity. This may critically alter the drug's overall effectiveness, possibly directly through the change in the particles' physical characteristics, possible by changing the longevity of the drug in circulation. The clear results generated by the nCS1, with more detailed and more accurate information than those reported by DLS, are thus critical for the manufacturer of this product - Spectradyne's nCS1 readily provides high-quality information that is unobtainable by standard techniques.

SUMMARY

Spectradyne has developed a powerful new platform for the size and concentration analysis of nanoparticles in a liquid sample. The nCS1 is ideally suited to serve applications in drug delivery and development, including the high-resolution characterization of particle formulations, the detailed analysis of formulation stability, and the quantitative assessment of the effects of process parameters on the quality of the final product. The instrument can measure a wide variety of different materials, and, of great importance to expensive and difficult-to-produce products, generates clear results using an extremely small sample volume of a few microliters. ◆

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BIOGRAPHIES

Dr. Andrew N. Cleland is the John A. MacLean Sr. Professor for Molecular Engineering Innovation and Enterprise at the University of Chicago, Faculty Director of the Pritzker Nanofabrication Facility, and recipient of Science magazine's 2010 Breakthrough of the Year. A leading authority on nanotechnology, Dr. Cleland is active in design and process development as Scientific and Technical Advisor at Spectradyne.

Dr. Jean-Luc Fraikin executed the initial development of Spectradyne's instrumentation as part of his PhD work in Dr. Cleland's group at UCSB. He has expertise in cancer cell biology, biochemistry, and in the application of microfluidics-based platforms to molecular diagnostics. As Chief Scientist at Spectradyne, Dr. Fraikin leads the development of instrument fluidics, software, and overall system integration.

Dr. Peter Meinhold earned his PhD in Physics from UC Berkeley and, as an experimental astrophysicist at UCSB, is an expert in low noise electronics and signal analysis.He has expertise developing compact instrumentation for space, where measurement failures cannot be tolerated, and in extracting cosmological signals with amplitudes orders of magnitude below instrument noise. As Chief Engineer at Spectradyne, Dr. Meinhold leads development of instrument electronics.

Dr. Franklin Monzon, prior to co-founding Spectradyne with Drs. Cleland, Fraikin, and Meinhold, spent 14 years in the semiconductor industry in various operations and product development roles. He has broad expertise in manufacturing and process development and earned his PhD from Caltech and his MBA from UCLA Anderson. Dr. Monzon leads operations, sales, and business development efforts at Spectradyne and is active in the production of the microfluidic cartridge.

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IMMUNOTHERAPY RESEARCH

The Shift Toward Combination Therapies

By: Jean Pierre Wery, PhD

INTRODUCTION

Traditional cancer treatments, such as radiotherapy and chemotherapy, are effective at treating many different types of cancer and remain the backbone of current therapy. However, they can be aggressive, are associated with serious side effects, and are vulnerable to treatment resistance. Improved understanding of cancer pathogenesis has given rise to new treatment options, including cancer immunotherapy, which takes a more targeted approach.

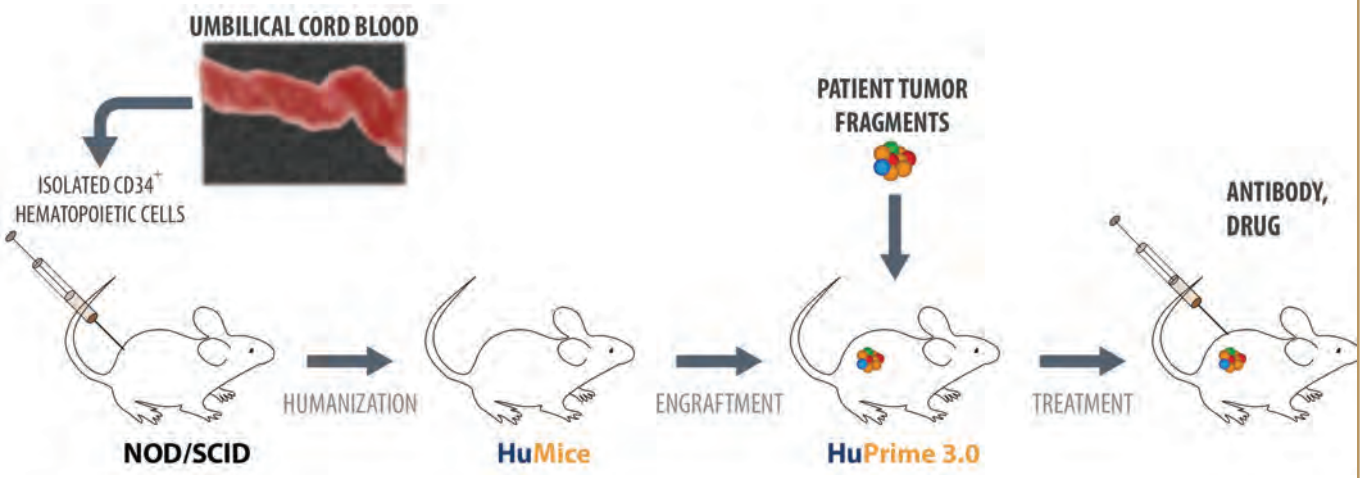
Immunotherapy focuses on the ability of an individual patient's immune system to eliminate or control cancer. Immunotherapy in combination with traditional treatments has the potential for becoming a more effective alternative to the current standard of care. These types of combination therapies are currently under investigation and appear to have synergistic effects compared to the use of one therapy alone and produce more durable results.

Combination therapies require further research and the development of new immunotherapeutics, as well as new treatment plans. Currently, there is an unmet need for improved preclinical models, with functional immunity, to drive forward immunotherapy research in oncology and to enable the successful transition of immunotherapeutics from the laboratory to the clinic. The use of appropriate research models can accelerate new compounds to clinical trials or help repositioning existing compounds. This could enable the identification of the right patient population for each new drug before they are tested in the clinic, reducing high attrition rates. At the same time, preclinical models can be used to test different treatment strategies, often involving more than one agent, and select the most appropriate regimen to drive forward, improving patient comfort and saving lives.

TRADITIONAL CANCER THERAPY

Chemotherapy and radiotherapy kill rapidly dividing cells, preventing the growth of a tumor, but they may also affect healthy cells within the patient's body. Most tissues have a reserve of pluripotent cells that are able to reactivate and start dividing and differentiate to replenish damaged or old cells. These cells, much like cancer cells are targeted by chemotherapy and radiotherapy and are not exempt from being damaged, causing severe side effects. Moreover, patients treated by traditional systemic chemotherapy as well as radiotherapy are prone to developing resistance in a fashion that is highly dependent on the tumor cell type, with some tumor being highly chemo- or radio-resistant. Traditional preclinical irradiation studies utilize simple single-beam techniques or whole body irradiation with lead shielding to focus the radiation to a specific area. However, the lead shielding does not ensure 100% protection to the tissues surrounding the tumor, and damage may occur. These settings no longer mimic treatment in the clinic as the dose or irradiation is much higher compared to what is given to the patient. A more sophisticated preclinical platform is now available, the image guided micro-irradiation (IGMI), to ensure a more targeted treatment with limited damage to surrounding healthy tissue and to reproduce in the lab with higher fidelity the clinical protocols.

FIGURE 1



PDX models, which are derived directly from human cancers, are at the forefront of personalized medicine research, enabling the identification of the right compound for the appropriate patient population before new drugs are tested in the clinic.

IMMUNOTHERAPY

The ideal treatment for any disease is one that can cure or prevent it from spreading with minimal impact on the patient's quality of life. Taking advantage of the immune system to fight cancer through the stimulation of a robust immune-based anticancer response by vaccination, or by attempting to inhibit factors that are currently blocking that response is showing promising results. Only in recent years, with a better understanding of the mechanism of action of immune cells, has progress started to be made in the application of immunotherapy to cancer patients, reducing side effects while increasing the efficacy of administered active compounds.

Currently, further research and new immunotherapeutics are needed before immunotherapy becomes a treatment accessible to all cancer patients. But with up to 95% of cancer drugs tested in Phase I trials not reaching a marketing authorization, the development of new drugs is costly and inefficient.1 The application of immunotherapy as a first-line treatment is still surrounded by few regulatory issues, the most palpable being the need to justify the higher costs of immunotherapies versus other therapies. Moreover, it still remains to be understood why some patients and tumor types do not respond to immunotherapy, hence there is a pressing need to discover novel biomarkers to predict response. Current clinical studies are addressing the possibility of combining immunotherapeutic agents with other therapies, such as targeted agents, to obtain more durable responses and avoid patients relapse.

The discovery of crucial molecular pathways that promote tumor growth and maintenance together with the development of drugs that specifically inhibit these pathways has ushered in a new era of cancer medicine. Antibody therapies, such as the anti-PD-1, anti-CTLA-4, and anti-PD-L1 antibodies, are currently the most successful form of immunotherapy.2 Programmed Cell Death 1 (PD-1), Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4), and Programmed Death-Ligand 1 (PD-L1) are endogenous proteins that naturally down-regulate the immune cells to prevent autoimmune diseases. The use of an antibody that binds to these proteins prevents this negative feedback and has been exploited for keeping the immune system alert to fight cancer. Cell-based therapies, or "cancer vaccines" represent another branch of immunotherapy, involving the isolation of immune cells from a patient's blood or tumors. The cells are activated, grown, and re-infused into the patient, where they are expected to mount an immune response against the tumor. This approach, known as adoptive cell transfer (ACT), has been restricted to small clinical trials so far; however, treatments using these engineered immune cells have generated some remarkable responses in patients with acute lymphoblastic leukemia (ALL) or lymphoma.

ACT building blocks are patient-derived T cells that have been modified

"The vulnerability of current therapies to treatment resistance has resulted in a shift from mono-agent approaches to combination therapy. Hitting one oncogenic driver at a time in cancer cells, where several regulatory networks are altered, allows them to escape treatment by rewiring to alternative pathways or acquiring additional mutations that confer insensitivity to treatment. Combination therapies target more than one signaling node at the time and often achieve more durable responses."

in vitro (CAR T cells) to express chimeric antigen receptors (CAR). These are able to specifically recognize and bind tumors antigens, inducing tumor cell death.

Current research focused on optimizing this approach emphasizes effective tumor targeting with limited off-tumor toxicity, optimized cell manufacturing to improve efficacy, and modulation of the host or cell product to increase in vivo persistence.[3]

The combination of traditional treatment and immunotherapy has shown to exert an additive effect on tumor growth inhibition over single-agent therapy alone, and can increase the number of cancer-fighting immune cells in the tumor.

COMBINATION THERAPY

The vulnerability of current therapies to treatment resistance has resulted in a shift from mono-agent approaches to combination therapy.

Hitting one oncogenic driver at a time in cancer cells, where several regulatory networks are altered, allows them to escape treatment by rewiring to alternative pathways or acquiring additional mutations that confer insensitivity to treatment. Combination therapies target more than one signaling node at the time and often achieve more durable responses.

Moreover, recent advances and the availability of IGMI has resulted in more accurate targeting of patient tumors and sparing of normal tissue with an associated reduction in side effects. This opens up the opportunity for multiple combination strategies of chemo- and radiotherapy. Interestingly, although radiotherapy has long been thought to be immunosuppressant, a refinement of the irradiation protocols and the availability of more sophisticated technologies, such as the IGMI, has opened up the possibility of combining radio and immunotherapy. Radiotherapy alone is often not sufficient to trigger antitumor immune responses, especially in poorly immunogenic cancers. However, the combination of radiotherapy with immune modulators, such as the checkpoint inhibitors, may have the capability to escalate antitumor responses to a level that could suppress or eliminate cancer. Combination therapy approaches are currently under investigation for many cancer types, including prostate, breast, and lung.

An example of combination therapy is the recent approval by the European Commission of vemurafenib and cobimetinib as a treatment for patients with metastatic melanoma. In the study, 495 patients received either vemurafenib or a combination therapy. The progression-free survival with the combination was around 12 months versus 7 months for vemurafenib alone. After 17 months, 65% of patients receiving the combination remained alive compared to 50% for single-agent treatment. The overall survival was 22 months with the combination treatment and 17 months with vemurafenib alone, representing a 30% reduction in the risk of death.

The approval of this combination was described as an important milestone in the development of new treatments that can help patients with advanced melanoma. Clinical trials continue to assess vemurafenib with cobimetinib for patients with melanoma, including a Phase II study. Additionally, a Phase Ib study is exploring the combination with the PD-L1 inhibitor, atezolizumab.4

Combining hormone therapy with radiation can help some men with early

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stage prostate cancer live longer. In one study concerning radiotherapy and short-term androgen deprivation for localized prostate cancer, the health status of nearly 2,000 men with low- and intermediate-risk prostate cancer were monitored. The 10-year survival rate for men who received the combination therapy was 62%, compared to 57% for men who received radiation therapy alone. Researchers also found that only 4% of the men who received combination therapy died of prostate cancer compared to 8% of those who received radiation alone.[5]

Alternatively, it has been found that, while treatment for non-small cell lung cancer uses a combination of two chemotherapeutics, adding a third drug does not add much benefit and is likely to cause more side effects. Single-drug chemotherapy is sometimes used for people who might not tolerate combination chemotherapy well, such as those in poor overall health or the elderly.[6]

MODELS

Efforts to maximize the benefits from immunotherapeutic agents are being limited by a distinct lack of experimental immunotherapy models that feature a functioning immune system. Developing effective immunotherapeutic drug treatments requires patient-relevant models with which to screen potential candidates. Moreover, due to the huge diversity and complexity of cancer, large collections of surrogate models are compulsory.

At present, the majority of experimental cancer models are composed of human tumors grown in immunocompromised mice. These are often derived from in vitro immortalized cancer cells, which allow researchers to follow the continuous evolution and malignancy of cancers and understand the biology of tumor development. These methods have been immensely helpful in studying how candidate compounds interfere with particular genetic mutations or pathways. But, immortalized cell lines are often selected based on their ability to grow, thus the debate over how well they represent a patient's tumor that must engage in complex interactions with its environment in order to grow is always ongoing.

The ability to maintain and study immortalized cell lines in vivo has proved to be a valuable tool in cancer research for several decades. The most widely studied models have been cell line-derived xenografts (CDX). Both athymic nude mice and mouse xenograft models that use human tumor cell lines have been used to increase understanding of factors affecting tumor growth. As an integral step in oncology drug discovery process, CDX models provide key decision-making information and a biologically relevant platform, to study disease progression, develop novel therapies to improve treatment options, and allow an agent to move forward from preclinical trials.

Using patient-derived xenograft (PDX) models to perform human surrogate trials are at the forefront of targeted medicine research. Xenograft tumor models from patient-derived tumor tissue (PDTT), engrafted into immunocompromised mice, conserve original patient tumor characteristics, such as genotype, tumor vasculature, and architecture. This results in a model far more closely aligned with a patient's disease, allowing the assessment of tumor evolution and response to therapy, the identification of the correct compound for each patient population before new drugs are tested and biomarker identification.

Both PDX and CDX are extremely useful tools for studying the physiopathology of human tumors and investigate the response to standard-of-care agents in a live host. But these models are just part of the solution to translating knowledge between clinical research and the clinic. To study the effects of immunotherapeutics, it is necessary for the host to have a functional immune system.

Syngeneic and Genetically Engineered Mouse Models (GEMM), with functional murine immunity, are available and widely used in immunotherapy research. Syngeneic models are mouse tumor cell lines growing in the same strain of mice in which the tumor originated, which provide an effective approach for studying how cancer therapies perform in the presence of a functional immune system. These models offer several undeniable advantages. They are relatively unexpensive, reproducible, and, unlike many current models, grow in immunocompetent hosts. As syngeneic tumor models have long been used in cancer research, there is a strong baseline of drug response data, and they come in a wide variety of tumor types. The models are also readily available, so studies are easily conducted with statistically meaningful numbers of mice per group.

Using these models in preclinical

trials allows researchers to determine the effectiveness of combination therapies involving traditional cancer treatment and immunotherapy while mimicking human disease.

SUMMARY

There is a current need for preclinical tools that can significantly improve the qualification of candidates at a much earlier stage in the drug discovery process. PDX, CDX, GEMM, and syngeneic models can all contribute by offering a unique opportunity to study immunotherapy within a human tumor microenvironment, helping to move the most promising anticancer compounds to the clinic and reducing drug attrition rates by selecting the best clinical strategy.

These models are driving immunotherapy research, which reduces off-target side effects and allows treatment responses to last longer by inducing immune cells memory. The use of immunotherapy in combination treatment has provided promising results, improving the effects of traditional treatments alone and reducing treatment resistance. With the right models, preclinical trials can move faster, attrition rates can be the lowered, and the process of drug development can be cheaper and more efficient.

Immunology is forever seeking new and improved ways to offer patients an improved quality of life and the end goal potential cures. Models can potentially transform cancer treatment and perhaps provide cures for cancer forms that historically had very poor survival rates. Combining immunology with anticancer agents solves the challenge of drug resistance and enables a stronger anticancer effect. ◆

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BIOGRAPHY

Dr. Jean Pierre Wery, prior to joining CrownBio, was Chief Scientific Officer at Monarch Life Sciences, a company dedicated to the discovery and development of protein biomarkers. Prior to joining Monarch, he spent 3 years at Vitae Pharmaceuticals, Inc., where he was VP of Computational Drug Discovery. Before joining Vitae, he worked for 12 years at Eli Lilly and Company in various scientific and management positions. Dr. Wery earned his BS and PhD in Physics from the Uinversity of Liege, Belgium. Following his PhD, he completed post-doctoral studies at Purdue University with Prof. Jack Johnson. Dr. Wery has authored more than 50 abstracts and publications.

LIPID NANOPARTICLES

EnCore™: Facilitating Delivery of RNAi Therapeutics to Treat Cancer

By: Marc T. Abrams, PhD, and Bob D. Brown, PhD

INTRODUCTION

Throughout the past 3 decades, human genetic data and preclinical models of cancer have facilitated identification of several oncogenes, such as MYC, CTNNB1, KRAS, and BCL2, as well-validated targets for new anticancer therapies. Conventional therapeutic modalities (eg, small molecules and monoclonal antibodies) offer only indirect and thus far inadequate solutions for targeting these oncogenes. For example, small-molecule delivery platforms would target post-translational modification or regulation of RAS family oncogenes, as opposed to directly inhibiting the function of these proteins. Although indirect MYC inhibitors, such as those targeting BET bromodomain proteins and cyclin-dependent kinase 7 (CDK7), have entered early clinical development, these agents are known to inhibit expression of many genes in addition to MYC, and therefore may have unwanted pharmacological activity in patients.[1,2] Given the failure of such indirect approaches to offer therapeutic benefit in the past, as well as the uncertainty whether they will ultimately be successful, their well-validated oncogenic targets were heretofore considered "undruggable."

The advent of RNA interference (RNAi)-based therapy offers the ability to home in on these targets directly. By enabling targeting at the messenger RNA (mRNA) level, as opposed to the protein level, RNAi allows treatment to focus on any expressed RNA in the genome, conferring advantages of potency and specificity through direct targeting of oncogenes. With RNAi, therapy can be directed at the transcriptional component of the tumor cell, including mRNAs, which encode proteins, as well as non-coding RNAs. Indeed, the power of RNAi lies in "druggability": the treatment plan can aim at any significant tumorigenic or tumor-related cancer target, yielding therapeutic benefits.

Prior to the advent of therapeutic RNAi programs, most small nucleic acid drug discovery programs relied on RNase H-active antisense oligonucleotides (ASOs). These ASOs, composed of single-stranded, chemically modified DNA and RNA, enabled the targeting of any cellular RNA for destruction of the RNase H enzyme. The process relied on hijacking the RNase H enzyme to mediate the effects of antisense therapeutics. Unfortunately, the antisense field suffered from the limited number of chemistries that could be applied to the therapeutic platform, while maintaining potency and tolerability, as well as from various pharmaceutical delivery challenges. However, the research, manufacturing, and clinical advances made during the pursuit of antisense therapeutics have greatly benefited the clinical application of RNAi.

The RNAi approach co-opts some functions of the natural RNA-induced gene-silencing pathway, using highly chemically modified double-stranded oligonucleotides to create a therapeutic platform that is chemically and structurally flexible. RNAi works via an efficient catalytic mechanism, yielding a high level of intrinsic potency. With such inherent properties, RNAi has the potential to achieve therapeutic success against previously undruggable oncogenic targets.

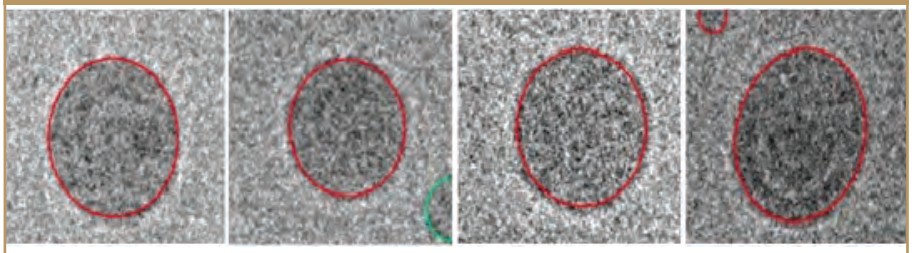
Nevertheless, efficient delivery of RNAi therapeutics to tumors can be challenging. One key challenge lies in the

inherent instability of RNA caused, in part, by our natural defenses against potential viruses.

If an RNAi trigger is administered intravenously without chemical stabilization or encapsulation within a nanoparticle, it will be degraded by nucleases in the blood and other tissues in a matter of minutes. Additionally, whereas most conventional small-molecular drugs are lipophilic, enabling their permeability across cell membranes, RNAi therapeutics are much larger and membrane-impermeable and therefore require a delivery solution. Even when chemically stable, RNAi molecules cannot be dosed systemically without incorporating delivery technology due to their molecular properties. In addition, because they are below the glomerular filtration size limit (approximately 5 nanometers), RNAi therapeutics are excreted through the kidney in minutes unless they are engineered to bypass this effect.[3] Such rapid excretion can compromise these molecules' tumor bioavailability.

Throughout the past decade, multiple research organizations have employed a delivery technology by which a small-molecule ligand, called N-acetylgalactosamine (GalNAc), is attached chemically to the RNAi therapeutic to mediate delivery of nucleic acids to the liver. This approach, which Dicerna Pharmaceuticals, Inc. is using in its DsiRNA-EX conjugate platform, is designed to direct the therapeutic payload to liver cells, where receptors on the hepatocytes recognize and bind to the ligand, pulling it out of the bloodstream. Unfortunately, despite many attempts, this ligand-mediated approach is not useful for delivery to tumors; to date, no ligand-receptor system expressed universally by tumors has been discovered that would enable this type of direct targeting with sufficient specificity. However, nanoparticle technology has the potential to enable tumor bioavailability even in the absence of a targeting ligand.

FIGURE 1



Electron microscopy image of individual Encore LNPs. A solid core, which is structurally distinct from previously reported liver-centric LNPs, is visible.

LIPID NANOPARTICLES: THE RNAi DELIVERY SOLUTION FOR TUMORS

Lipid nanoparticles (LNPs) offer a three-part RNAi delivery solution. The first is encapsulation of the active pharmaceutical ingredient (API), which in this case, is the RNAi therapeutic. Encapsulation within LNPs endows the API with pharmaceutical properties that enable delivery to the site of action. The LNPs can protect the RNAi therapeutic from degradation, rapid excretion, and liver clearance. Encapsulation also facilitates tumor bioavailability, due to the achievement of a plasma half-life of sufficient time to enable uptake in the tumor. With LNPs, tumor uptake may occur more efficiently than in other tissues because of the leaky vasculature in the tumor environment (an effect described in the field as "enhanced permeability and retention," or EPR). Although the molecular mechanism of LNP uptake into tumor cells is not fully elucidated, it is known to be very different from the mechanism of LNP uptake in the liver.

The second part, penetration of the tumor, is considered a potential advantage of LNP technology. Certain LNPs enable passage of the RNAi trigger through the vascular layer of the tumor to achieve extravasation into the tumor parenchyma. In other words, the LNP not only gets through the first layer of tumor cells, but it is eventually distributed throughout the tumor, homogeneously.

Internalization into the tumor cell is the third step in LNP-based delivery. This property enables trafficking through the tumor cell so that the RNAi trigger eventually reaches the cytosol of the cell, which is where the RNA-induced silencing complex (RISC) – the endogenous RNAi machinery – is located. Engagement and activation of the RNAi molecule within RISC triggers silencing of the target mRNA.

The utility of previous LNP technologies for tumor-directed delivery was limited by the fact that the LNPs either did not accumulate in the tumor at a high enough concentration, or conversely, accumulated in the liver at a level that resulted in unacceptable toxicity. Those previous platforms, which almost invariably arose from liver-directed LNP programs that were

retrofitted for tumor delivery, did not mediate efficient delivery of RNAi into the cytoplasm of tumor cells. All liposomes have some degree of filtration out of the liver (which itself is designed to filter out particles), compromising their ability to deliver a therapeutic payload to the tumor. We have also learned through experimentation that the parameters that drive delivery to liver tumors differ greatly from those driving delivery to normal liver cells.

Another limitation of previous LNP technologies is that the liposomes were originally developed as hollow spheres containing a volume of water (ie, an entrapped aqueous space). Indeed, early publications included illustrations depicting free RNA floating inside a liposome "balloon." From a chemistry and physics perspective, that theoretical structure was utterly incompatible with the particle components: the structure incorporated a highly negatively charged RNA payload with pencil-like rigidity, mixed with positively charged lipids.

ENCORE™ LNP TECHNOLOGY: OPTIMIZING TUMOR-DIRECTED DELIVERY

Dicerna's EnCore™ LNPs have been designed and optimized for delivering RNAi therapeutics to tumors. All optimization work was performed in tumors instead of first achieving maximum activity in the liver and then making marginal modifications to achieve tumor delivery. This approach is more expensive and labor-intensive because pharmacology models are required for tumor delivery, but it has yielded preclinical data demonstrating knockdown of key oncogenes.[4,5]

Development of the EnCore LNP technology started by taking the screening approach of particle delivery efficiency and RNAi activity, measuring target knockdown in tumor tissue. After evaluating several "off-the-shelf" single-stranded antisense delivery platforms, Dicerna concluded that none would be functional for double-stranded RNAi. Based on that evaluation, the company decided not to use mouse liver as a surrogate tissue for tumor delivery. Although widely available, inexpensive, and easy to deliver to the liver, normal whole animal tissue is not comparable to tumor tissue. Dicerna therefore decided to focus on a different target tissue with completely different structural, biochemical, and surface properties not comparable to any normal organ.

Another key difference of EnCore LNPs is that their LNP structure is solid, not hollow. They contain a solid core of positively charged lipid, with RNA inside. The well-controlled aggregate makes consistently shaped, solid spheres. The core's purpose is to bind RNA efficiently, without wasting payload, and to protect it from the environment (ie, during the manufacturing process as well as in vivo).

Other LNP manufacturing approaches for delivering RNA mix all components in a single step. Every component of the particle must solve all independent variables simultaneously: spontaneous aggregation; organization into a sphere that is mechanically and chemically stable; administration into a vein; mediation of biodistribution through the blood; accumulation in target tissue; and delivery of the payload to the cytoplasm. If the particle has poor stability in a vial while stored in the pharmacy, and if any component is tweaked, that variable change ripples through the entire process, creating many challenges.

To overcome such mechanical and initial manufacturing challenges, Dicerna divided the LNP development process into two discrete elements to achieve in vivo pharmaceutical functions: an RNA lipid core and the addition of a thick layer of additional lipids surrounding the core surface. The additional lipids were selected not only for their mechanical properties or manufacturability in loading RNA efficiently, but for biodistribution, specific tissue uptake, and their ability to transfect or mediate delivery of RNA into the cytoplasm of cells. Hence the EnCore name, a portmanteau of Envelope and Core.

VIABILITY OF MYC AS A THERAPEUTIC TARGET

As one of the first discovered oncogenes, MYC is possibly the single-most well-validated oncogenic target, and it remains one of the most extensively studied. Recent mechanistic insights have sparked a resurgence of interest in MYC. Although it has been known for approximately 30 years as causal for tumorigenesis and tumor maintenance, new functions of MYC are constantly being unraveled. In terms of human genetics, a growing body of evidence suggests MYC is involved in >50% of all human tumors.[6] Indeed, its targetability appears to be near-universal: the more MYC is studied, the more it appears to be upstream of many of Hanahan and Weinberg's "hallmarks

of cancer."[7]

Preclinical studies show that DCR-MYC, an RNAi therapeutic delivered via EnCore LNPs, inhibited gene transcript activity and reduced tumor volume in multiple mouse models of cancer. Interim results from an ongoing Phase 1 dose-escalation study of DCR-MYC, presented at the 2015 ASCO annual meeting, demonstrated good tolerability and early signs of clinical anti-tumor activity and metabolic responses across various dose levels in patients with advanced solid tumors, multiple myeloma, and lymphoma, supporting early validation of MYC as a therapeutic target.[8]

The available DCR-MYC data suggest that RNAi may offer a novel and viable strategy for directly targeting MYC. Preclinical models suggest that effective delivery of the MYC RNAi trigger results in significant mRNA knockdown, functional suppression of MYC protein, and by extension, potential therapeutic benefit. For those reasons, Dicerna selected MYC as the oncogenic target for its first EnCore clinical development program.

POTENTIAL FUTURE APPLICATIONS

EnCore LNPs can be used to deliver other RNAi payloads to tumors. For example beta-catenin is another well-characterized, well-validated oncogenic target with abundant human genetic and preclinical evidence.[9-11] Dicerna is developing a second-generation EnCore LNP that appears to hold promise for delivering beta-catenin Dicer substrate short-interfering RNA (DsiRNA) molecules to achieve functional knockdown in many tumor types.

The modular nature of the EnCore LNP technology is one of its strengths. With a delivery platform that can mediate delivery to various tumor types, Dicerna can "mix and match" EnCore LNPs with different RNAi payloads. When fully realized, matching of payload to tumor type may therefore potentiate a tailored approach to treatment of genetically defined cancers. ◆

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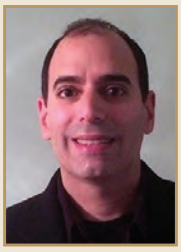
BIOGRAPHIES



Dr. Marc T. Abrams has served as Senior Director, Preclinical Development at Dicerna since January 2014. He works with his team and colleagues on advancing RNAi platform technologies, developing preclinical drug candidates for specific therapeutic areas, and clinical translation of biomarkers. From 1997-2013, Dr. Abrams has worked at Merck and Co., Inc. in numerous R&D roles, including Research Fellow, Staff Biochemist – Oncology, Senior Research Biochemist - Oncology, and Associate Director - RNA Therapeutics. Dr. Abrams earned his BS in Biotechnology from Drexel University, his MS in Biology from the University of Rochester, and his PhD in Biochemistry from Thomas Jefferson University. He has authored or co-authored 13 peer-reviewed publications in the RNAi field.

Dr. Bob D. Brown joined Dicerna Pharmaceuticals as Chief Scientific Officer and Senior Vice President (SVP), Research in 2008. He leads the discovery and nonclinical development of RNAi-based therapies, including an agent targeting the MYC oncogene, which entered clinical trials in 2014. Prior to joining Dicerna, Dr. Brown was the Vice President of Research and Technology at Genta, and he worked on more than 75 issued patents and patent applications. Dr. Brown works directly with clinicians and study investigators on trial design, execution and interpretation of results. He earned his PhD in Molecular Biology from the University of California, Berkeley, and his BS degrees in Chemistry and Biology from the University of Washington.

DRUG DELIVERY

PLEX™ Local Drug Delivery Platform Enables Prolonged, Controlled-Release Medications

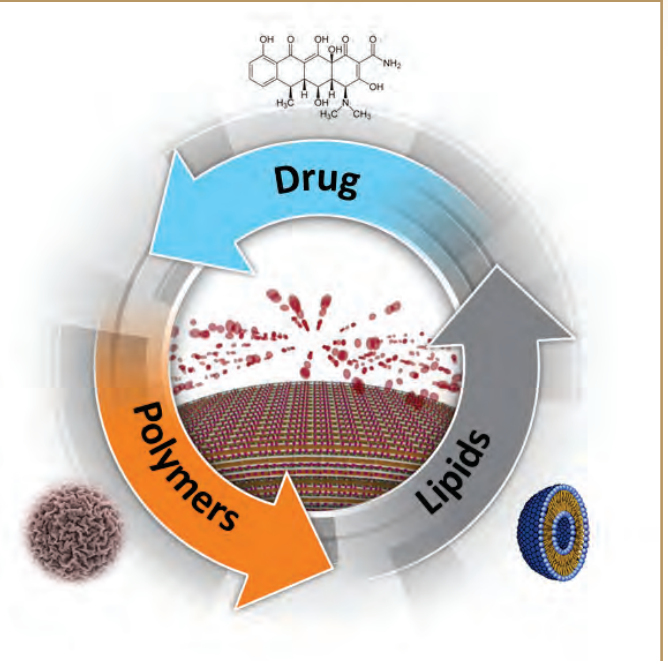
By: Noam Emanuel, PhD, Chief Technology Officer - PolyPid

INTRODUCTION

Common drugs are molecules that act via an interaction with their target molecule, within a specific location, in order to generate a specific therapeutic change. While systemic drug delivery is relatively convenient, it is often difficult to reach the target location due to limited extravasation from the bloodstream into the target tissue. There is often a need for higher dosages over time in order to maintain the requisite local concentration during the treatment period, which sometimes is not possible. The need for higher dosages increases the risk of toxicity and adverse side effects, which in some cases, are beyond acceptable limits. The situation becomes even more challenging when blood supply is minimal or preliminarily destroyed due to trauma or surgery. To overcome this major limitation, it is desirable to deliver active ingredients locally, targeting the medication directly to the disease site. This can be done by implanting a drug reservoir directly into the target area, and releasing the drug over the desired period and rate so as to be effective, while at the same time - non-toxic. Although highly desired, the release duration from the current local treatments is often too short to be effective. Furthermore, the release rate is often not controlled, and therefore, efficacy is compromised, and the risk of potential toxicity remains.

An optimal drug delivery system should be able to release drugs at a rate and profile that will support efficacy and reduce or eliminate potential toxicity, and should be able to do so over sufficient duration. Currently used drug delivery

FIGURE 1



PLEX™: Polymer-Lipid Encapsulation matriX

systems typically utilize either polymers or lipids, commonly in the form of liposomes. Whereas some of the polymer-based local drug delivery systems feature a long-lasting release, they also have the drawback of an initial high burst release. On the other hand, even though a liposome-based drug delivery system features a low burst release, it is still limited to a short-lasting release period.

Biodegradable polymers, such as poly (lactic-co-glycolic acid) (PLGA), chitosan, or collagen were tried as local drug delivery platforms. However, in many key indications, such

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polymeric drug delivery systems cannot maintain a constant and sufficient release rate of antibiotics over the prolonged period of time needed to fully eradicate the invading bacteria, for example.

Another major aspect that needs to be noticed is the stability of the entrapped drug within the reservoir. This is especially important to support the prolonged delivery of sensitive drugs. This major characteristic is not well covered by the current polymer-based local delivery, leading to the loss of the drug earlier than needed.

The PLEX™ (Polymer-Lipid Encapsulation matriX) platform is a matrix made of the combination of lipids and polymers (Figure 1). The substructure comprises alternating layers of polymers and lipids that entrap a therapeutic drug between them in order to form a protected reservoir that enables an effective localized drug delivery at the target site. The PLEX matrix protects the drug reservoirs in vivo, and enables prolonged delivery of sensitive drugs over periods ranging from days to several months.[1] The application of PLEX technology enables optimizing drug treatment regimens by predetermining release rates as well as durations, a rare combination of attributes.

CONTROLLED & PROLONGED DELIVERY

The use of overall low drug doses is highly beneficial, from both safety and economic perspectives. The primary challenge is finding the right balance between administering low doses without compromising efficacy (Figure 2). PLEX significantly enhances efficacy by optimizing bioavailability of the active ingredient and permits the use of smaller drug doses over prolonged periods for greater safety. PLEX's key attributes include the following:

Flexible Entrapment: The ability to accommodate many types of drugs, such as small molecules, peptides, proteins, and nucleic acids. Additionally, unstable and delicate drugs, such as heat-sensitive drugs and drugs that are sensitive to some organic solvents, pH levels or enzymes can also be encapsulated by PLEX. PLEX enables constant, controlled, prolonged delivery of all these different types of drugs.

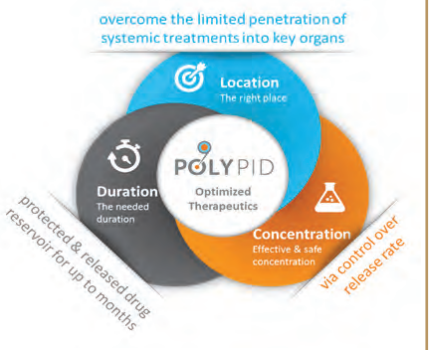
Protected Reservoir: PLEX features a unique drug reservoir that protects the integrity of the encapsulated drug throughout its prolonged exposure to the hostile environment in the body, both from biological and water-related destruction.

Control Over the Release Profile: PLEX avoids an undesired effect of uncontrolled drug bursts resulting in enhanced safety and a preserved long-term reservoir.

Release Rate: PLEX can be predetermined to optimize the release rate of each drug according to the desired medical need. The release rate can be set to be a constant rate (zero-order kinetic) for most of the drug reservoir if so desired (Figure 3).

Release Duration: In order to improve efficacy, PLEX enables a predetermined and optimized drug-release period ranging from 1 day to several months.

FIGURE 2



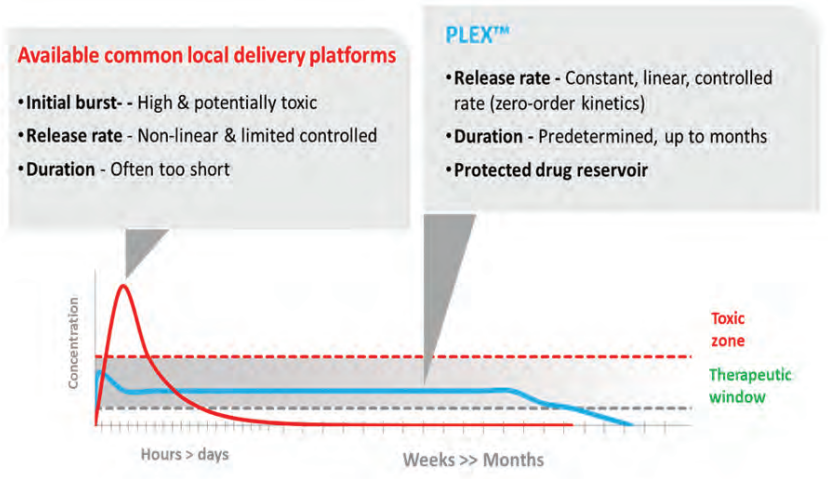
PLEX™ platform - optimized therapeutics for local delivery.

Flexible Design: The technology permits local drug delivery in stand-alone products or even as coatings of medical devices, implants, or other substrates.

PLEX™ PLATFORM - BREADTH OF DRUG APPLICATIONS

Over 20 different drug types were encapsulated using PLEX, each of which demonstrated controlled zero-order kinetics release over prolonged periods. These include small molecules, such as dexamethasone, NSAIDs, and doxorubicin, peptides, proteins, and nucleic acids (Figure 4). The advantages of our PLEX drug delivery system lie in its unique combined characteristics and attributes. The power of the PLEX technology is due to a unique combination of characteristics: a protected reservoir; a pre-designed release profile and controlled release rate; and the ability to tailor release duration. The power of PLEX is also in its versatility. It is suitable for use with many types of drugs ranging from small molecules and peptides, to proteins and even siRNA. The PLEX matrix can also enable the use of multiple drug types in

FIGURE 3



Controlled and prolonged delivery.

a variety of combinations. Along with these combined advantages, the use of PLEX is also very practical from an industrial point of view. This is reflected by the following:

Off-the-Shelf Compounds: PLEX is composed of well-known components which are commercially available and extensively used in the pharmaceutical industry.

Supports a Simple Regulation Process: PLEX is composed of commercially available ingredients. No covalent bonds are created during the self-assembly of PLEX, either with the drug or between the formulating materials.

Simple & Mild Production Techniques: Production is performed under mild physical conditions and is based on self-assembly of chemical substances while synthesis is not required. The process is cost effective.

ANTI-INFECTION PORTFOLIO

BonyPid-1000™

PLEX was validated in clinical settings via BonyPid-1000™, a PLEX based product comprising antibiotics loaded synthetic bone substitute intended for filling bone voids or defects while supporting an antibacterial protected bone healing process. BonyPid-1000 contains a broad-spectrum antibiotic (doxycycline) to reduce microbial colonization on the bone void filler. BonyPid-1000 has completed a clinical trial in severe open fractures indications, demonstrating excellent safety and efficacy results, including 0% infections in the target fractures and 0% amputations after 6- 12-month follow-up (vs. an average of 25% and 7%, respectively, demonstrated in a historical control group and known literature).

Bone bacterial infection may result in bone destruction. Bone infections are difficult to cure due to the bone's poor accessibility to systemically administrated antibiotics. This problem is compounded due to the fact that currently available local delivery systems may not be sufficiently effective due to their high burst and short lasting effect (Figure 5).

The clinical results in the use of BonyPid-1000 demonstrate that the 1-month release of doxycycline in a controlled manner provides a new, effective way for treating open fractures.

BonyPid-1000's success attests to the safety and effectiveness of PLEX as a delivery system and indicates its applicability in other medical situations associated with local infections, such as in treating diabetic foot ulcers, infected implants, etc.

BonyPid-500™

BonyPid-500 is a synthetic, doxycycline-eluting bone graft substitute, based on ß tri-calcium phosphate (ßTCP) granules. BonyPid-500 is intended for use as a bone grafting material to fill, augment, or reconstruct periodontal or oral/maxillofacial defect, such as filling of periodontal/infrabony defects, ridge augmentation, filling of extraction sites (implant preparation/placement), and sinus lifts and filling of cystic cavities, while at the same time providing local infection protection.

Upon hydration in the body, the PLEX matrix gradually degrades and allows the antibiotic entrapped within PLEX layers to be released constantly into its surroundings while the bone filler acts as a scaffold to support osteoconductive bone recovery.

BonyPid-500 gradually resorbs and is replaced with new formed natural bone during the healing process. The antibacterial activity of the released antibiotic takes place in conjunction to the osteoconductive activity of the bone substitute, and prevents its potential

rejection or early absorption by bacteria-related local bone infection. It also protects the surface of the graft from the development of biofilm. BonyPid-500 is now initiating clinical studies in patients with peri-implantitis.

D-PLEX™

D-PLEX is designed to combat Surgical Site Infections (SSI), which are the second most common hospital-acquired infections (HAI) and are considered a serious complication of surgical procedures. Such complications often lead to prolonged hospitalization, repeated surgeries, and may sometimes result in death.

D-PLEX is based on our PLEX platform and will provide a safe and effective local anti-bacterial (doxycycline) treatment of tissues or organs by administering a localized and protected drug reservoir during surgical procedures.

After implantation, the reservoir constantly releases the entrapped antibiotic over several weeks. In doing so, the D-PLEX reservoir allows for prolonged infection management and effective antibacterial activity, including management of hospital or community-acquired resistant bacteria that were most recently classified by the US government as a serious global threat.

Most recently, the US government classified community-acquired resistant bacteria as a serious global threat. In a rabbit study, PLEX-doxycycline coated implants were found to eradicate even doxycycline-resistant S. aureus bacteria.[2]

FIGURE 4

PLEX™ fits any size or physical characteristics.

RESEARCH PROGRAMS

Anti-Inflammation

Systemic treatments are very effective for the treatment of inflamed conditions. However, wide use of anti-inflammatory agents is limited due to serious systemic side effects that include liver damage, heart disease, addiction, and pain. We are developing a PLEX based platform for localized and controlled delivery of a very small, yet effective, dose of dexamethasone that carries minimal systemic side effects.

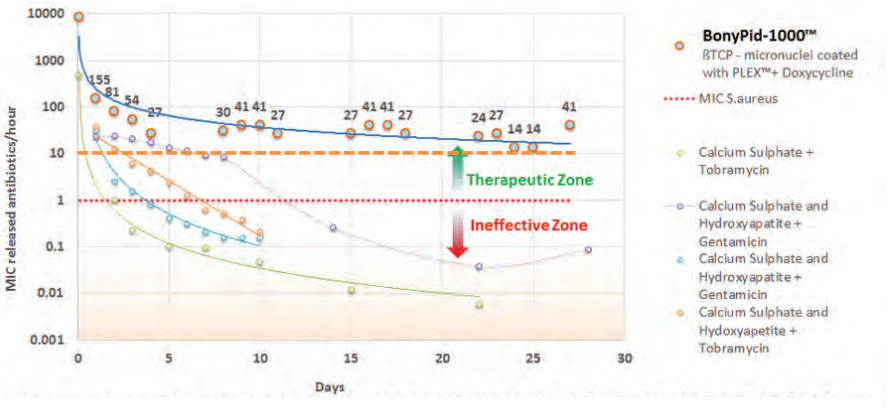
We have demonstrated safety and efficacy of a dexamethasone agent in a small animal model, thus completing a full pre-clinical package.

Anti-Cancer

Systemic anti-cancer treatments have serious side effects. Our program is designed to treat cancer by extended localized release of common chemotherapeutic agents, such as doxorubicin. The program is aimed at reducing the overall dose of toxic agents for a prolonged local delivery, while achieving effectiveness that is at least comparable to systemic administration.

We have successfully demonstrated eradication of cancerous cells in an animal model.

FIGURE 5



BonyPid-1000™ - PLEX™ offers superior drug release profiles. Release measured in MIC per hour (in-vitro). The release profiles of currently available delivery systems were adapted from published data. MIC = Minimal Inhibitory Concentration. This reflects the lowest drug concentration that prevents bacterial (S.aureus) growth.

Protein-Based Products

Current growth factors solutions have serious side effects, such as excessive bone growth. Our program, Growth Factors (BMP-2), is designed to promote bone growth by extended localized release of PLEX-formulated BMP-2 in spinal fusions or voids. By using only 1% of the overall commonly administered systemic dose in a prolonged, local delivery, we minimize potential side effects while achieving superior in vivo efficacy.

The potential therapeutic effect of various antibodies has been intensively studied throughout the past decades, and a variety of diseases and clinical disorders are treated by the administration of such drugs. A technological barrier to the use of antibody-based drugs is the need for practical, effective means for their local delivery location where blood supply is limited. Monoclonal antibodies were successfully encapsulated in PLEX, and were continuously released in vitro for at least 15 days. Animal studies are planned to start soon.

PARTNERSHIP OPPORTUNITIES

Pharmaceutical and biotechnology companies continuously develop new drugs to address the ever-changing medical landscape and health threats.

However, many of the new drugs suffer from toxicity concerns or from limited systemic administration bioavailability that impede their safety and efficacy.

Additionally, companies are looking for ways to extend exclusivity of their proprietary products, particularly in connection with drugs that are approaching patent expiration.

PolyPid's proprietary platform, PLEX, is a protective drug encapsulation platform that allows a controlled, local release rate over extended periods of time (up to months). We have proved the versatility of our PLEX platform with preclinical trials and in some cases of clinical trials, using a variety of small molecules, peptides, and proteins. Partnering with us will provide companies with a targeted, local drug delivery vehicle that will optimize a drug therapeutic payload and clinical outcome, and where applicable, help overcome a looming patent cliff.

SUMMARY

PLEX is a unique local drug delivery platform that brings numerous innovative solutions to the market in various fields, such as infections, inflammations, and cancer.

Infections, and specifically, management of antibiotic-resistant bacteria, are a global health concern to which there is no effective solution at the moment. PLEX offers ways to combat this. Our strengths include an experienced management team, world-class drug delivery R&D expertise, broad IP protection, and organizational flexibility. ◆

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BIOGRAPHY

Dr. Noam Emanuel is Chief Technology Officer of PolyPid. He has vast experience in biotechnology projects, including development of drug delivery systems and immunology. His extensive expertise includes immunotherapy, vaccines, immunodiagnostics, systemic and local drug delivery, and medical devices. Dr. Emanuel has a number of approved patents in the field of drug delivery and diagnostics. He is a Co-founder of PolyPid and served as its CEO during the company's first 3 years. He earned his PhD from the Faculty of Medicine at the Hebrew University of Jerusalem.

Special Feature

Outsourcing Formulation Development & Manufacturing: Using a Single Provider Reduces Costs & Risk

By: Cindy H. Dubin, Contributor

The depth and breadth of outsourcing by pharmaceutical/biopharmaceutical companies realized last year is expected to expand significantly in 2016, particularly with regard to formulation development and manufacturing activities. In fact, a recent survey from That's Nice finds that 69% of the pharma/biopharma respondents expect to increase their use of contract development and manufacturing providers (CDMOs).

The survey identified the following as the primary reasons for this anticipated increase:

- A pipeline of drug candidates that is more robust than has been witnessed in more than a decade;
- An increasing rate of FDA NDA/BLA approvals, with 2014 and 2015 seeing near-peak numbers and similar levels expected going forward, largely due to the greater number of accelerated approval pathways (Fast Track and Breakthrough Therapy Designations and Accelerated Approval and Priority Review processes);
- The growing number of biologic drugs in development, many by traditional pharma companies that lack biotech expertise;
- The entrance of numerous small, virtual startups into the market that have no manufacturing capacity;
- The increasing complexity of both small- and large-molecule drugs, such as poorly soluble compounds, antibody-drug conjugates (ADCs) and highly potent Active Pharmaceutical Ingredients (APIs), that require

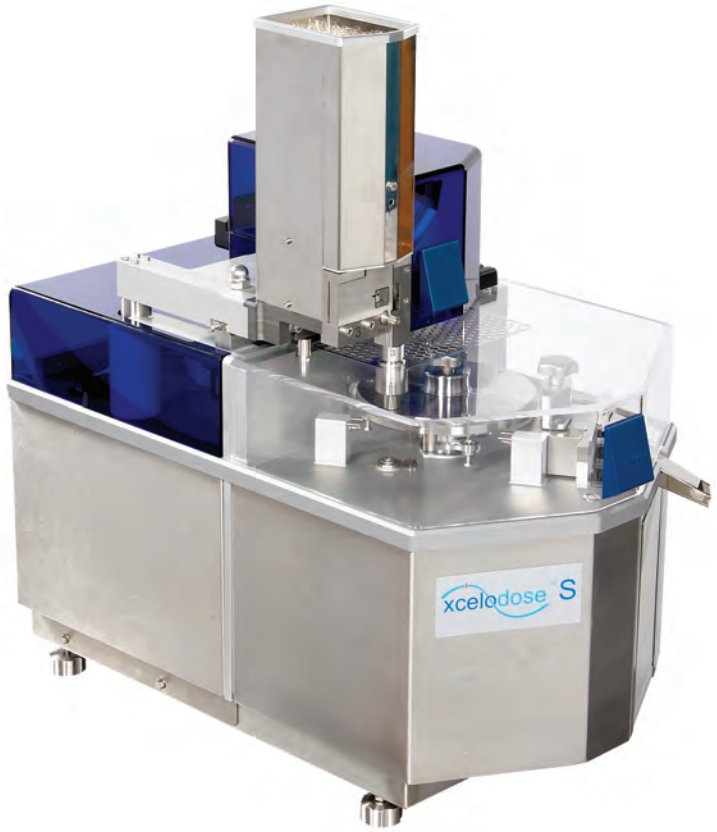
Lipid multi-particulates in a sprinkle capsule shell that can be utilized for pediatric formulations (Xcelience).

specialized facilities, equipment, and operational expertise; and

- The movement away from blockbusters, many of which have or will soon fall off the patent cliff, to small-volume, niche and targeted treatments that require unique skills and expertise.

As pharma/biopharma companies look to expand their use of outsourcing in the areas of development and manufacturing, they want to do so with a single provider. Approximately 40% of the survey respondents believe it is very important to use a one-stop-shop CDMO to fulfill their needs from R&D through to commercialization.

This annual *Drug Development & Delivery* report highlights how CDMOs are evolving their models to become their clients' single provider and to accommodate their more potent, challenging products.



This Xcelodose 600s micro-encapsulation machine at Almac helps negate a need for expensive and time-consuming tablet/capsule development.

Almac—A Single-Provider Model From Trials to Commercialization

Traditionally, biotech and virtual companies have embraced integrated drug substance and drug product services. Now, with Big Pharma looking to both rationalize internal capabilities and consolidate their supplier base, these companies are embracing an integrated services approach within their outsourcing model.

Almac offers a full suite of drug substance and drug product development and manufacturing services, including processing of highly potent materials. "All services are delivered from a single site, thereby reducing risk and cost while simultaneously expediting time to the clinic," explains Brian Eastwood, Head of Business Development (Europe), Almac. "Vendor management is simplified, allowing our clients access to single-project management teams covering chemical and pharmaceutical development."

Within development, as pharma companies seek to address the need for pediatric versions of their new chemical entities, formulation development and clinical manufacture of minitablet presentations are on the increase. This dosage form, whether filled in sachet, capsule or bottle, offers the benefit of increased dose accuracy and flexibility, as required for the pediatric population.

Almac, in partnership with its clients, has recently expanded its minitablet capabilities through the purchase of mid- to high-speed encapsulation machines, capable of filling minitablets, powders, and pellets into capsules. "In addition, the acquisition of both a stick pack machine and additional standard sachet filling technology has given our clients access to this in-demand dosage form for pediatric presentations," says Mr. Eastwood.

Highly potent API production at CordenPharma Colorado.

In addition to the pediatric population, continued focus on oncology therapies has led many CDMOs to develop and manufacture dosage forms for highly potent molecules. "We are witnessing a transition to low-dose API in-capsule presentations for Phase I and, in some instances, Phase II clinical trials within the oncology field," he says.

To meet this increasing demand, Almac has acquired a third Xcelodose 600s micro-encapsulation machine. "This API in-capsule route accelerates time to clinic, negating a need for expensive and time-consuming tablet/capsule development, with the added advantage of significantly reducing API burn for early-stage development."

Recently, Almac partnered with a US-based client for the development of both the API and formulation of drug product. Having manufactured clinical, registration, and process validation batches, Almac now produces the commercial product from its UK headquarter facilities.

"By leveraging our integrated API and drug product expertise, prior to and through NDA submission and approval, our client was able to take advantage of a single-partner approach with smooth transition through the drug development process and commercialization, saving time, transfers, and other uncertainties inherent in a multi-supplier process," says Mr. Eastwood. "By doing so, Almac played an integral part in bringing a much needed treatment for a previously unmet medical need to the market."

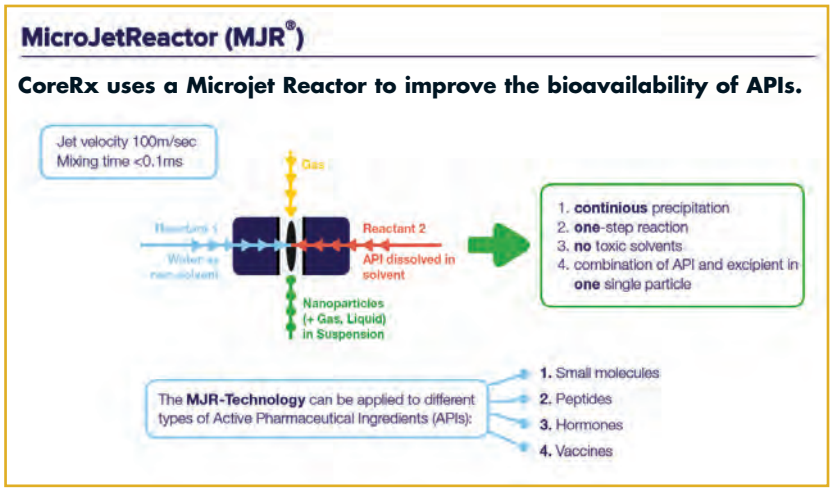
CordenPharma—Full-Service Capabilities Geared to Meeting Aggressive Timelines

CordenPharma has seen increased outsourcing activities for formulation development and manufacturing, especially in some niche or specialized technologies (e.g. contained products such as antibiotics, oncology, highly potent, etc.). Due to this higher demand, pharmaceutical customers have moved towards shorter preferred supplier lists for development and commercial manufacturing. To meet the demand, CordenPharma is expanding capacity in all R&D groups, both in terms of personnel and equipment, explains Luca Porcu, Director, Global Small Molecules Platform, CordenPharma International.

CordenPharma provides full-service contract development and manufacturing to customers from early development (Phase I clinical studies) to commercialization. "Spanning from cGMP intermediates to APIs to final drug products, CordenPharma's integrated supply is especially effective for products in the clinical phase, where customers are looking for more flexible timelines, with preference to managing a unique supplier," says Mr. Porcu. To fill the gaps of existing market needs, CordenPharma is investing in new development and commercial capabilities and capacities, including the acquisition of new manufacturing facilities, which are also focused in forward and backward integration.

CordenPharma works closely with customers to provide a comprehensive development plan for all clinical phases to achieve product compliance, quality, and safety. "In addition, a Quality by Design (QbD) approach enables customers to gain robust manufacturing processes that will provide a stable supply throughout the development and commercialization phases, while still meeting their often very aggressive timelines," he says.

One recent development and manufacturing project involved support in meeting a customer's market demands for patients to gain or maintain access to their product after a shortage. The project required quick response time and expertise in all related production and regulatory activities. "CordenPharma was selected for our ability to manage on very short notice, with a flexible, dedicated team that successfully provided a documentation package that enabled favorable and fast approval by the relevant health authority," explains Mr. Porcu. The approval was granted without need of a pre-approval inspection, resulting in an immediate restoration of supply to the customer's patients.



CoreRx—Simple to Complex Formulation Handling

Formulation strategy has shifted in the last few years towards direct compression and roller compaction. Moving away from wet granulation, which is costly and has more potential issues with product stability, however, is still a necessary evil for dosage forms with high percentages of API that are not amenable to processing by any other method.

"To facilitate this switch, CoreRx has embraced the more highly designed excipients from either a particle engineering or co-processed perspective for both immediate- and modified-release dosage forms," says Brian McMillan, Vice President and Chief Technology Officer, CoreRx. These include co-processed excipients such as Retalac and Parteck SRP-80 for modified-release formulations and Prosolv and Kollidon VA-64 for immediate-release dosage forms.

In some cases, enabling polymers to be used for direct compression where they previously could only be used for wet granulation can lead to more rapid formulation development, he says.

In addition to enhancing release profiles, CoreRx is focused on improving API solubility. "These APIs require more processing for particle size reduction, solid/spray-dried dispersion preparation, lipid complexation, and nanoparticle preparation in order to improve bioavailability," says Janice Cacace, Director Formulation Development, CoreRx. "For these processes, we recently acquired a microfluidizer and a Microjet Reactor."

For solubility enhancement and modified release, solubility/dissolution screening can become a burdensome

task. Six months ago, CoreRx acquired a Pion Rainbow fiber-optic system that can be used for real-time solubility and dissolution screening. "Because this is real time, and does not require the use of HPLC on the back end, the turn-around time has been decreased from days to hours," she says. "This rapid screening technique has become very important to us in the early formulation development stages."

Metrics Contract Services—Flexibility, Simplicity, & Scalability

Metrics Contract Services (MCS) is embarking upon a $65 million oral-solid dose site expansion, scheduled to become fully operational in late 2017. The expansion will double the current clinical manufacturing footprint and offer dedicated non-GMP development lab space for small-scale formulation development, GMP clinical trial materials for both pilot and mid-scale batch manufacture, and GMP commercial-scale manufacture. "The site expansion will increase our potent and non-potent commercial capacity by more than six times, and the expanded facility will position Metrics Contract Services to meet client needs ranging from Phase I to commercial," says Thomas B. "Brad" Gold, PhD, Vice President of Pharmaceutical Development, Metrics Contract Services.

Dr. Gold points out that flexibility and simplicity are key to successful formulating and manufacturing of clinical trial material batches at Metrics Contract Services. "We can accelerate timelines and provide drug candidates to clinics more quickly. Often, we choose to employ simple API-in-capsule using our Xceledose simple formulation capsules or tablets for First in Man (FIM) Phase I clinical studies, depending upon the API physicochemical characteristics and clinical timeline. We have the ability to manufacture GMP batches at very small scale (100g). This is useful when API availability is limited, which is common in early project stages."

Regarding flexibility, a dedicated development area helps initiate projects quickly; within two weeks or less following contract approval. Potent-capable manufacturing suites in the R&D and the clinical manufacturing areas accommodate OEL Category 3 compounds. Granulators and supporting fluid bed dryers can be used for batches ranging from 1kg to 400kg; roller compactors for batch sizes as small as 10g facilitate continuous batch processing; blenders handle batch sizes between 100g to 450kg; and tablet presses and encapsulation equipment on the R&D and clinical manufacturing side are capable of scaling up to commercial equipment.

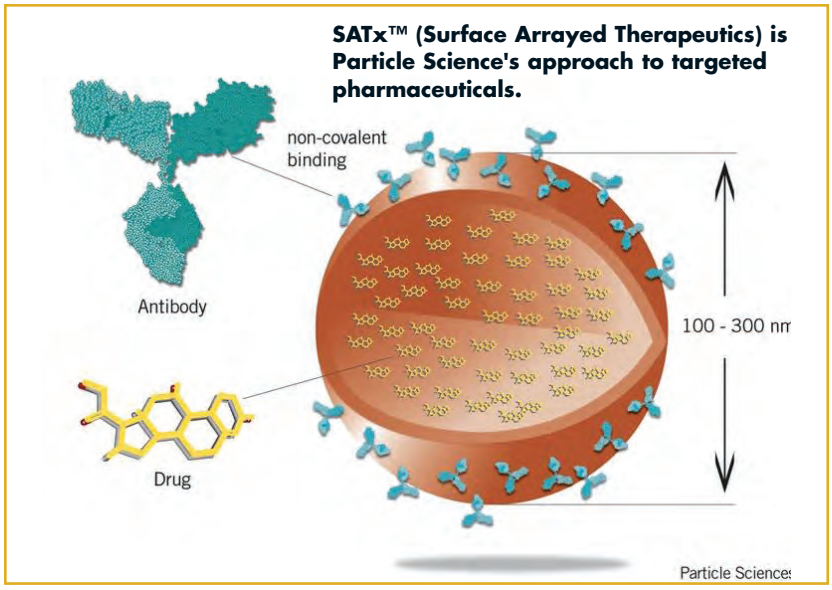
The ability to scale up projects successfully is demonstrated in this late Phase I/early Phase II project that Metrics Contract Services handled a few years ago. "The client was managing multiple changes in the development/clinical timeline and API, something many companies experience with projects at that stage of drug development," explains Anshul Gupte, PhD, Associate Director of Pharmaceutical Development at Metrics Contract Services.

MCS provided analytical development and manufacturing support, and produced the clinical trial supplies throughout the Phase II and large Phase III trials. "To accommodate clinical requirements, we scaled up the formulation from 1kg to 400kg batch size, largely done while the product was still being manufactured under GMP, as API supply was limited along the way," says Dr. Gupte. Several QbD studies were conducted at various scales.

"The client recently had the drug product approved for commercialization in both the United States and the European Union," states Dr. Gupte.

Particle Sciences—Targeted Drug Products Using Nano Formulations

More and more CDMO clients are demanding a model that provides end-to-end solutions. With the acquisition of Particle Sciences (PSI) by Lubrizol LifeSciences, PSI now offers exactly this–starting from polymers, through formulation development, and into commercial manufacturing on a global scale. "This minimizes the cost and risk of tech transfers plus shortens overall development timelines," says Robert W. Lee, PhD, VP, Pharmaceutical Development Services at PSI. "We also have established relationships with other providers offering



SATx™ (Surface Arrayed Therapeutics) is Particle Science's approach to targeted pharmaceuticals.

complementary services, including pre-clinical *in vivo* testing."

PSI has a repertoire of formulation technologies focusing on BCS II and IV molecules. Dr. Lee says there are only a handful of viable drug delivery approaches–particle size reduction, amorphous forms, permeation enhancers, lipidic and polymeric systems, etc.–but each has different flavors and one size does not fit all.

One area of growth for PSI is in the formulation of biologics. "We can use standard delivery methods for biologics and have also developed proprietary approaches, including SATx™, which is our approach to targeted pharmaceuticals, and can be used for therapeutics as well as vaccines," explains Mark Mitchnick, MD, CEO of PSI.

Targeted drug products are a key objective of pharmaceutical development, especially since the advent of monoclonal antibodies. These targeted pharmaceuticals are typically composed of monoclonal antibody-drug conjugates (ADC). ADC technologies, however, do have several challenges that have limited and slowed their development and commercial use. New formulation technologies that use nanoparticles circumvent these limitations. In fact, more than 100 different APIs can be encapsulated by solid lipid nanoparticles (SLNP), claims Dr. Mitchnick. Physicochemical attributes can be tailored through inclusion of surfactants into the formations. The resulting particles can interact with either the hydrophobic or electrostatically-charged domains of amphipathic and hydrophilic molecules. These particles efficiently bind to, and are coated by, pharmaceuticals and bio-pharmaceutical molecules, and are being developed for monoclonal antibodies that target tumor cells and other tissues.

"These nanoparticle formulations effectively link biopharmaceutical and pharmaceutical molecules, like ADC, but without the need for, and limitations of, conjugation chemistries," says Dr. Mitchnick. "This results in final products with unique and useful physicochemical and biological attributes, including improved vaccine potency and safety, and targeted pharmaceutical and biopharmaceutical drugs directed against specific disease targets."

Velesco Pharmaceutical Services—Air-Filled Softgel Capsule Shells Overcome Challenges With Highly Lipophilic Compounds

Early-stage development of highly lipophilic drugs is considered challenging as such compounds typically have low and variable bioavailability, as well as questionable stability. In these cases, the traditional formulation strategy is to use liquid-filled softgel capsules. While generally this strategy is successful, it comes at a considerable cost as there could be a need to manufacture large batches due to equipment considerations with a commensurate high cost in terms of API utilization, says Lisa Crandall, MS, PMP, Associate Director CMC Project Management, Velesco Pharmaceutical Services.

"It is possible to manufacture one large batch of the lowest strength product and then dose subjects with ever increasing numbers of capsules to achieve higher doses," says Ms. Crandall. "This is not a tactic to be recommended as the excipients used in softgel capsule fills can, at larger

Hand-filled softgels from Velesco.

doses, cause significant gastro-intestinal side effects. Thus, the early development of highly lipophilic compounds is widely viewed as problematic and costly."

To address this challenge, Velesco Pharma has developed a strategy of hand filling pre-formed, air-filled softgel capsule shells. This allows small batches to be manufactured with minimal waste and, as there is little set-up, the batches can be manufactured quickly.

The initial pre-formulation and liquid-fill development activities for these capsules are no different than those conventionally followed. This has the advantage of allowing the liquid-fill vehicle's use in later, larger batches produced in the traditional manner. Having determined a suitable vehicle, and after qualifying the analytical methods, Velesco Pharma then prepares the first stability batches. These typically bracket the lowest and highest strengths envisaged by the client. Filling the capsules admittedly requires some dexterity and a steady hand, but the process is fairly straightforward, says Ms. Crandall.

The air-filled softgels look like regular filled softgels with the addition of a narrow, hollow "tail." Using a small syringe fitted with a very fine-bore needle, the liquid-fill solution is slowly introduced into the body of the shell. When the correct amount of liquid has been filled, the tail is sealed as close to the capsule body as possible by using heated forceps. In this way, batches of up to a few hundred liquid-filled softgel capsules can be prepared in a day.

The addition of a new, lower or higher dose to a stability program can be achieved quickly and at minimal cost both in terms of API and time needed to prepare the supplies. In the same way, as the clinical trial progresses, the preparation of additional, unforeseen strengths can be accomplished in a timely fashion with minimal expenditure of bulk drug.

As an example, one client, whose drug's initial estimated dosing range was originally believed to be less than 100-fold was able to dose over a 250-fold range as data became available during the study. The additional dose groups were added as the study progressed with the new supplies being made "just-in-time," the strength being based upon PK data from the previous dose group.

Xcelience, a Division of Capsugel Dosage Form Solutions—Bi-Layer & Multi-Particulate Formulations

There has been an increased interest in combination products, but there are challenges in developing these products, such as ensuring the two APIs will be compatible and if they need different release profiles. If it is found that a combination product can successfully overcome these concerns, then the product can be developed using several formulation development technologies, such as a bi-layer tablet approach, where one layer can have a controlled- or delayed-release profile and the other layer can have an instant-release profile.

"Xcelience currently offers the ability to make bi-layer tablets, and because of the increased interest in combination products, we are purchasing a second bi-layer tablet press so that our experimental formulation development lab will have its own tablet press," says Paul Skultety, PhD, Vice President, Pharmaceutical Development

Services, Xcelience, a division of Capsugel Dosage Form Solutions. "In this way, formulation development can be accomplished quicker and without interrupting clinical supply manufacturing. As the tablet presses are similar, it will make for a smooth transition from the formulation development lab to the GMP manufacturing facility."

Xcelience formulators can develop bi-layer tablets with the specific release profile required for the desired product characteristics. "We routinely develop and manufacture bi-layer tablets that have different release profiles for each layer," he says.

In addition to bi-layering, Dr. Skultety says there is greater focus on multi-particulate formulations for combination or single entity-products manufactured by either extrusion/spheronization or drug layering insert cores using fluid-bed technology. The APIs produced by either process can be manufactured into separate bead formulations and then encapsulated as the finished dosage form. If desired, the separate beads can maintain their own unique dissolution profile. Another approach is capsule-in-capsule technology, where a smaller pre-filled capsule is inserted into a larger liquid-filled capsule, each containing a separate active ingredient. Xcelience expanded its access to capabilities and product technologies in these areas when it joined Capsugel Dosage Form Solutions earlier this year.

Within the multi-particulate formulations space, there is growing interest in specialized applications such as lipid multi-particulate (LMP) technology for pediatrics. LMPs, which are produced using melt-spray-congeal technology, utilize a range of Generally Recognized As Safe (GRAS) lipid-based excipients to encapsulate active ingredients and achieve a high degree of palatability, as well as solubility improvement and/or controlled release—depending on the target product profile needs.

For pediatric use, beads produced by any of these processes can be encapsulated using sprinkle capsules. This allows for the beads to be emptied and sprinkled onto something like yogurt or applesauce.

"The advantage of the multi-particulate system is that it provides more flexibility in the dose range (by adjusting the fill amount of the beads) that can be developed, and it can be encapsulated with either a two-bead fill, or a bead fill with a powder fill," says Dr. Skultety. "We routinely perform extrusion/spheronization, fluid-bed processing, LMP, and mini-tablets in both the experimental labs and in GMP manufacturing. The resulting beads or tablets can be manufactured to have controlled-, delayed-, or targeted-release dissolution profiles using a matrix mechanism or by providing a membrane film coat to control the release."

As an example, a client was developing a bead-filled capsule utilizing extrusion/spheronization for a Phase I study. At the very last minute, the client needed to change the dosing in the Phase I study and go to a much broader dosing range. "Because of the flexibility of dosing beads in a capsule, Xcelience was able to adjust the lower starting dose from 10mgs to 5mgs and change the highest dose from 50mgs to 75mgs. This was accomplished with the same amount of API, and without the need for additional experimental work or interrupting the product schedule," explains Dr. Skultety.

Also under the Capsugel umbrella are Powdersize, Bend Research, and Encap Drug Delivery, which Xcelience can go to for help with troublesome APIs. For example, if the particle size of the API needs to be reduced, Powdersize can perform experimental trials with minimal amounts of API and reduce the particle size to the size required.

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Roger Kurinsky
Senior VP, Tubular Glass Americas
Gerresheimer

GERRESHEIMER

Gerresheimer in the US - Fully Focused on Core Business

Headquartered in Düsseldorf, Germany, Gerresheimer is a leading supplier of specialty glass and plastic products for the pharmaceutical industry. The product portfolio includes packaging and products for the safe, simple administration of medicines: insulin pens, inhalers, prefillable syringes, injection vials, ampoules, bottles, and containers for liquid and solid medicines with closure and safety systems as well as packaging for the cosmetics industry. Gerresheimer produces worldwide in more than 40 plants and is currently investing heavily in local production in the US. Drug Development & Delivery caught up with Roger Kurinsky, Senior Vice President of Tubular Glass Americas, to discuss recent strategy shifts, the importance of the US pharma market, and how Gerresheimer's investments in the US can benefit pharma companies.

Q: How important is the US market for Gerresheimer?

A:The US market is one of our original markets, and it's one of the keys to the entire Gerresheimer Group's leadership positions. Almost one-third of our total revenue will come from North America in 2016. We're the market leader in many segments there, and we're a sought-after partner to the US pharmaceutical industry. Throughout the past 18 months, we made substantial investments in our US production facilities so that we can deliver locally manufactured, high-level quality products to our customers.

Q: In 2015, Gerresheimer sold its tubing operations to Corning. Why did it decide to do that?

A: Gerresheimer is the number one manufacturer of glass packaging for injectable pharmaceutical drugs in the US market. Following a critical assessment of our portfolio, we unanimously agreed that production of tubing glass is no longer one of our core business operations. We will focus on the finished product, ie, the converted glass packaging product like vials, cartridges, ampoules, and syringes. In our plastics business, we buy granules to produce pharmaceutical plastic packaging. In our converted glass business, we now source tubing from Corning and other vendors. It gives us more time and resources to concentrate on our core portfolio. So that's why we sold our tubing operations in Pisa, Italy, and Vineland, NJ, to Corning. Corning is a leading manufacturer of diverse types of glass and a company that makes substantial investments in research and development. We know we can depend on them for excellent quality glass tubing in the future, which is why our two companies have concluded a long-term tubing supply agreement. We've also established a joint venture with Corning to drive innovation in the pharmaceutical glass segment. Specifically, we're going to be concentrating on what we do best; manufacturing packaging for pharmaceuticals in the same high-quality all over the world.

Q: Why are global quality standards important?

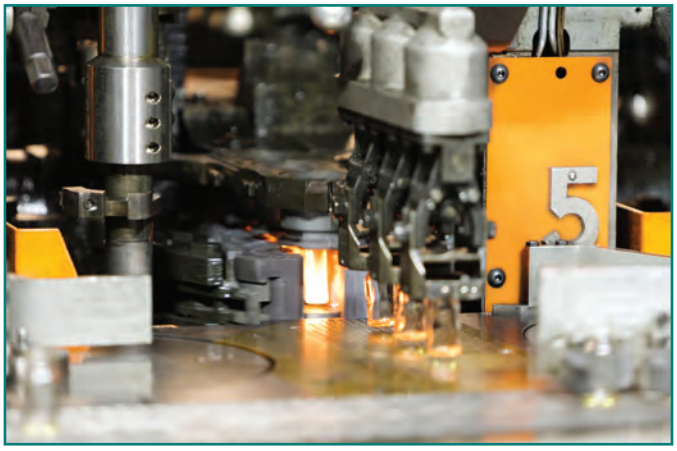
A: Let me give you an example. An American pharmaceutical company manufactures its active drug ingredient in India. It also has its filling lines there and wants a local pharmaceutical packaging manufacturer to supply it packaging. The final packaged pharmaceutical drug is then sent to the US where it is retailed. Obviously, the customer needs the vials made in India to be the same quality as vials made elsewhere. The FDA is increasingly inspecting pharmaceutical companies in China, India, and other countries if they manufacture drugs for the US market. Actually, Chinese regulators as well as the regulators in other countries have almost as stringent patient safety requirements as the US FDA.

Q: How does Gerresheimer ensure those global quality standards at its plants?

A: As an example, we manufacture vials for vaccines or oncological drugs at nine of our plants around the world. We decided to install standardized, state-of-the-art machine parks at all of these plants, and our ambitious several multi-year project involved investments running into the double-digit millions since 2014. We want to supply our customers with significantly improved vials with the highest possible quality. The latest generation of machines, controls, and inspection systems guarantees the same high Gerresheimer quality standards at every single one of plants around the world, so it makes no difference which one of them the customer procures its vials from.

Q: How did you organize the project?

A: We started off at our US plant in Morganton in 2014 by supplying and installing the new generation of machines there. Our people in Morganton are the best-in-class when it comes to vials. Soon afterward, we started installing the new machines at Morganton's sister plant in Vineland. That was in 2015. We provide training on the new machines to all the people at our other plants around the world onsite here in the US. The Querétaro plant in Mexico was next in line, also commencing in 2015, and all the new machines will be in place later this year. The European plants are scheduled for the machine



upgrades in 2016. We're currently in the process of building a brand new plant in Kosamba, India, and making preparations to install the new-generation machines at our Chinese plants.

Q: What type of machines does Gerresheimer use?

A: We're installing two types of vial manufacturing machines at our plants around the globe. The first was developed by our own engineers and built for our tubular glass plants by a partner. We sourced the second one from a European machine manufacturing company. These machine types are supplemented by the controls, inspections, and packaging systems, Gx G3, Gx RHOC, and Gx Thor, which were developed in-house and are part of a stringent TQM system that guarantees maximum precision and quality assurance in line with the latest standard.

Q: Last year, Gerresheimer's moulded glass plant in Chicago Heights underwent some major modernization work. Why is the Chicago Heights facility so important to Gerresheimer's operations?

A: We are the only company manufacturing Type I moulded glass vials in the US, and we do that at our Chicago Heights plant. Our customers want a local supplier that can meet their increasingly stringent quality requirements. One of the key objectives of the renovation project was to equip the plant for particulate-free glass packaging production. We have invested about $30 million in this project and are now in a position to offer our customers an ultra-modern production facility for high-quality, Type I moulded glass vials and bottles.

Q: What improvements did you make at Chicago Heights?

A: Quite a lot. The investment program was set up with the objective of meeting both present and future customer requirements as increasingly stringent standards are introduced. Investments in best-available production and inspection technology, and infrastructure optimization will give us higher levels of quality, the more efficient use of resources, and a better environmental footprint.
Both the furnace and the steel base underneath it have been replaced. The new furnace capacity is 20% higher, and it consumes substantially less energy per ton of glass. Raw material supply and batch house automation, plus modern furnace control systems, have significantly improved efficiency at the hot end. Two of the three production lines are new, and the third line underwent a general overhaul. Modern camera systems perform dimensional and visual inspections for early detection of non-conformities and defective products.

The higher production output after the conversions made a cold-end redesign and upgrade necessary. All inspections and packaging operations now take place in controlled environments, and all the in-line inspection systems have been modernized and standardized. The safe pack technology has been upgraded so that larger containers can also be shrink-wrapped. A new layout for the cold end has also reduced the number of actions involved in the packaging process, which reduces the potential for glass to glass contact.

Q: Why was particulate reduction an important mission of the modernization?

A: The FDA is strongly committed to eliminating particulates in injectable drugs to improve patient safety. Our customers in the pharmaceutical industry contribute to particulate reduction in their section of the supply chain, which involves washing, filling, and sealing, whereas our efforts are focused on manufacturing particulate-free glass packaging. So the Chicago Heights upgrade and conversion project aimed to re-engineer the plant to satisfy even the strictest particulate requirements. The project also saw the introduction of innovative and patented technology at the Chicago Heights plant. Moreover, optimizing furnace, feeder, and mold cleaning processes and the use of different materials have significantly reduced particulate contamination. State-of-the-art inspection systems also check the glass products for contamination and reject the ones that aren't up to standard before they are delivered to the customer.

Q: Gerresheimer acquired Centor in the summer of 2015. What does this mean for Gerresheimer?

A: The Centor acquisition was an important strategic milestone for us. At the same time, it was our most expensive acquisition ever. We'd been planning a stronger positioning in the medical plastic packaging segment for a while, and the Centor acquisition allowed us to achieve it. But this wasn't just a strategic decision, it was a business decision because Centor is a very profitable company. Since the Centor take-over, we have significantly expanded our pharmaceutical primary packaging business. Centor is the market leader in the North American consumer market for plastic packaging and closures for prescription drugs. It supplies a nationwide network of wholesalers, pharmacy chains, and supermarkets.

Q: Gerresheimer has a medical plastic systems plant in Peachtree City, GA. What are your plans for that plant?

A: We've been manufacturing diverse medical plastic systems in Peachtree City for many years now, and we also have a development and engineering center there. This year, we'll be commencing production of a new asthma inhaler for the North American market in Peachtree City. We finished the preparations last year by building another new production building, installing state-of-the-art cleanroom technology, the first injection moulding machines, and precision moulds, commencing the validation process, as well as installing and testing the assembly lines. Commercial production of the new inhaler will start soon.

Q: Why is Gerresheimer so confident its customers will approve of all the investments?

A: We talk to our customers, and we listen to them! Our teams of experts visit customers or customers visit us on an almost daily basis. At the end of May, we're inviting all our customers to the Gerresheimer Pharma Days event in Chicago so that we can discuss new developments with them. On the second day of the event, we'll be taking them on a visit to our Chicago Heights plant. We're also in the process of implementing our large-scale global customer survey to obtain detailed information about how our customers believe we can make improvements. So we're committed to continuous improvement. Not just in the US, but at all of our 40 plants around the world. ◆

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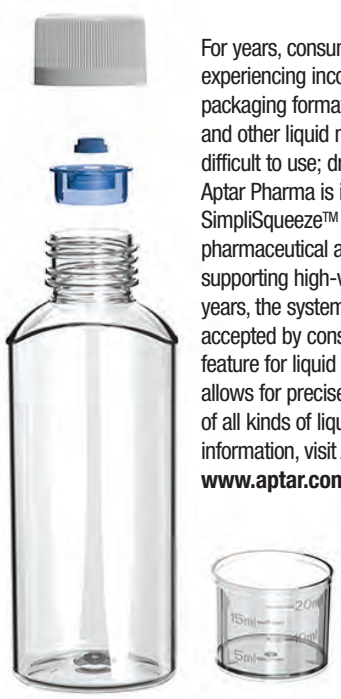
Technology & Services Showcase

Global CRMO

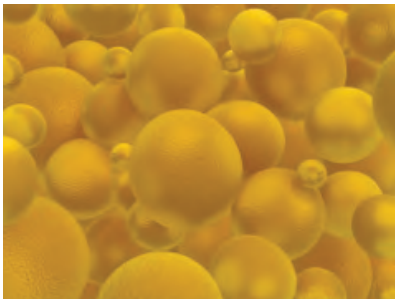
AMRI is a global contract research and manufacturing organization that has been working with the Life Sciences industry to improve patient outcomes and the quality of life for about 25 years. As part of its integrated services offering, AMRI provides comprehensive bench-to-market sterile drug dosage form development and manufacturing services. Supported by extensive expertise and integrated capabilities that span preformulation through commercial phases, we are equipped for the development through commercial scale production of complex liquid-filled and lyophilized parenterals, sterile suspensions, and ophthalmic formulations. Our comprehensive array of preformulation and formulation development competencies comprise material sciences, solubility enhancement, formulation screening, lyophilization development, and early clinical GMP supply. Our capabilities also include development and small-scale commercial manufacturing for your early to mid-clinical projects, and Phase III and commercial manufacturing. For more information, contact AMRI at or visit **www.amriglobal.com.**

Liquid Formulation Dispenser



For years, consumers and patients have been experiencing inconvenient and annoying packaging formats for cough and cold syrups and other liquid medications. Products are difficult to use; drugs cannot be dosed easily. Aptar Pharma is introducing its patented SimpliSqueeze™ technology for pharmaceutical applications. Successfully supporting high-volume consumer brands for years, the system has shown to be widely accepted by consumers as an added value feature for liquid products. SimpliSqueeze allows for precise and hygienic administration of all kinds of liquid medications. For more information, visit Aptar Pharma at **www.aptar.com/pharma.**

Nanoemulsion Formulations



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Technology & Services Showcase

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Technology & Services Showcase

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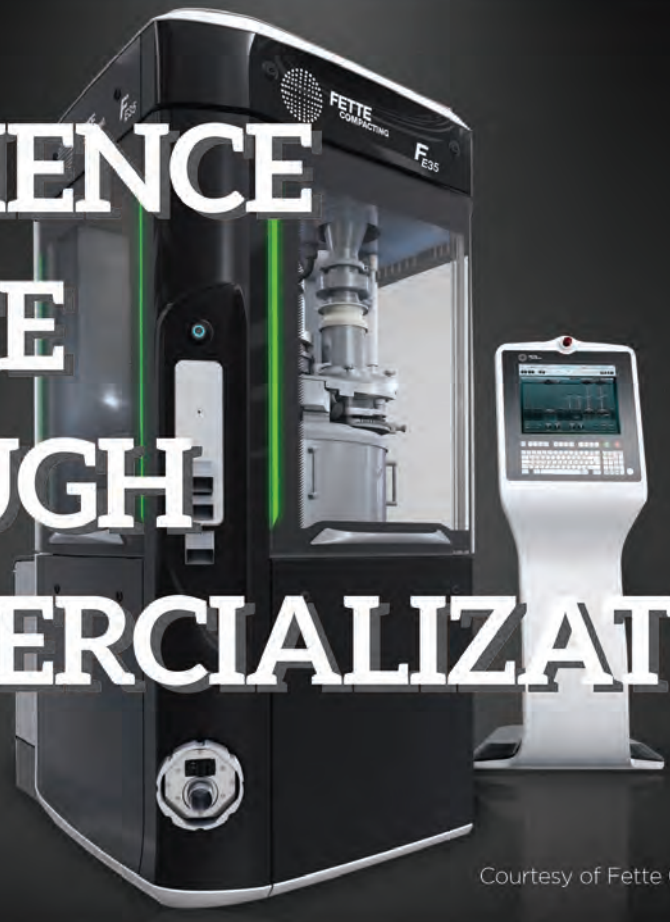
EXPERIENCE SCIENCE THROUGH COMMERCIALIZATION



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- Sterling Kline, Vice President, IPX Integrated Project Services

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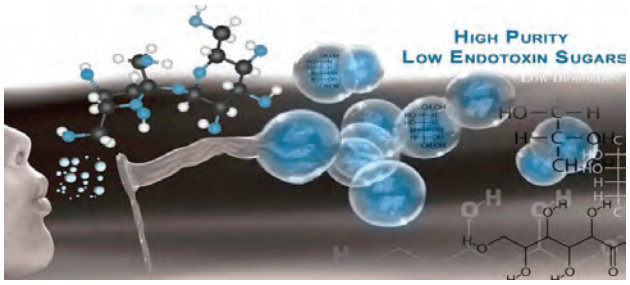

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Technology & Services Showcase

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MRI CONTRAST AGENTS

Could More Stable Soon Also Mean Safer?

By: Nadim Michel Daher, Frost & Sullivan

INTRODUCTION

A record-high attendance of 1,000 radiology directors and managers convened at the 2015 Annual Meeting of the Association for Medical Imaging Management (AHRA 2015) — and not just because it was held in Las Vegas. Radiology is going through interesting times. Under the coordinated care paradigm that is gradually emerging in the US, as well as all the changes forced on volume-based economic models. The medical imaging enterprises are under a great deal of pressure to redefine their goals and reassess their value.

The one main connecting thread that transpired from the AHRA 2015 sessions and show floor was Patient-Centric Radiology. Under this overarching theme, two main axes — care quality and patient safety, as well as population health — were central to our top three conference takeaways:

- Community-wide commitment to radiation dose reduction and patient dose monitoring continues, within and beyond the CT modality area. Interventional radiology, general radiography, and mammography are being integrated as part of more comprehensive multi-modality dose management programs. The urgency is mounting for having the means to bring nuclear and molecular imaging (SPECT, PET) into the picture as well.

- Low-dose Lung Cancer CT screening presents a major new opportunity for radiology to play a central and proactive role as part of broader population health management efforts. New screening programs are being developed at an increasing pace since the recent reimbursement approval by CMS, and will increase exponentially when the new associated CPT codes are actually released.

- Ongoing developments on the legislative front (Stark Amendment, Anti-kickback Statute, Sunshine Act), on the regulatory front (NEMA, Joint Commission, FDA, ACR) and on the payment front (fee-for-value reimbursements, capitation) are collectively stressing the urgency for more robust utilization management in medical imaging. This industry-wide push will be further reinforced by the Protecting Access to Medicare Act of 2014 (PAMA), while the CMS will materialise this mandate when it defines the appropriateness criteria (expected November 2015) and the approved mechanisms (expected April 2016) for advanced imaging clinical decision support (CDS).

Patient-centric radiology implies a deep transformation that touches every aspect of medical imaging operations. It is driving considerable changes in the way medical imaging services are ordered by physicians (online decision support), the reasons why they are ordered (data-driven appropriateness

"In 2006, major new clinical research findings brought to light a potentially harmful effect of Gadolinium-based compounds on the non-healthy kidney, linking its prolonged use with the development of nephrogenic systemic fibrosis (NSF). Several clinical studies concurred in raising a red flag on the use of MR contrast agents on patients with kidney insufficiency, which rapidly materialized into new clinical guidelines to exclude these patients from any contrast-enhanced MR procedure."

criteria), the way they are delivered (within multi-disciplinary care teams), the way they are perceived (as a cost driver needing justification), and the healthcare providers' expectations from these services (to add value to population health efforts throughout the care continuum).

As importantly, the shift to more patient-centered care delivery models elevates the patient to the forefront of medical imaging's value proposition. Patients are gaining influence and becoming an additional stakeholder to reckon with in imaging decisions. They are being empowered as part of population health efforts, while being more penalized for driving healthcare costs upward through higher co-pays. In this context, patients are being addressed more directly through targeted marketing efforts (low-dose, comfort, cost savings, screening compliance), are gaining more pricing transparency as consumers of imaging services, and are growing more aware of the risks and benefits of various imaging procedures.

While radiation dose continues to steal the show in the patient safety arena, significant new clinical research is shedding a spotlight on contrast agent safety, particularly in the area of magnetic resonance imaging (MRI). These ongoing developments are further strengthening the rationale for not limiting these efforts to radiation dose alone, but for monitoring and managing contrast doses as well.

GADOLINIUM-BASED CONTRAST AGENTS & PATIENT SAFETY, A CLEAN RECORD UP UNTIL 2006

Awareness about the toxicity of Gadolinium is not new. Gadolinium-based compounds, the most commonly used agents for contrast-enhanced MRI, have always been known to have potentially toxic effects if Gadolinium is left free-floating in the human body. This occurs, if and only if Gadolinium molecules were to be released from their wrapping structure, the chelate, before being evacuated in urine.

However for the longest time, it was believed commercial Gadolinium-based contrast agents (GBCAs) used chelates robust enough to wrap Gadolinium long enough to fulfill its entire journey, from intravenous injection through ejection by the kidneys. These GBCA compounds were thought to leave the body without leaving a trace, and they were considered an efficient, risk-free pharmaceutical that fulfilled its role as a contrast agent without any harm or drawback.

2007 & THE KIDNEY BLACK BOX WARNINGS

In 2006, major new clinical research findings brought to light a potentially harmful effect of Gadolinium-based compounds on the non-healthy kidney, linking its prolonged use with the development of nephrogenic systemic fibrosis (NSF). Several clinical studies concurred in raising a red flag on the use of MR contrast agents on patients with kidney insufficiency, which rapidly materialized into new clinical guidelines to exclude these patients from any contrast-enhanced MR procedure. These guidelines were enforced through a black box warning by the FDA on May 23, 2007, which affected every existing GBCA product on the market without making any specific distinction between each individual product.

For obvious reasons, this blanket approach to a regulatory measure was not well received by the industry vendors. Under European guidelines, one argument put forth by its detractors, categorizes patients into low-, medium-,

and high-risk patients, there are still three GBCA products approved, even for high-risk patients. Further, some vendors attest that none of administered doses containing their product can be linked to NSF or other kidney disorders.

FAST FORWARD TO 2014: RISING SAFETY CONCERNS ABOUT HEAVY METAL BRAIN RESIDUES

During 2014 and 2015, a new series of breakthrough clinical research findings from various parts of the globe came in to disrupt the lay of the land in the GBCA marketplace. Several studies originated over the past 18 months from Japan (the Kanda study from Teikyo University of Medicine, Tokyo), Italy (the Errante, Mallio, and Quattrocchi study) and Germany (the Gries study from Heidelberg Medical Center). Collectively, these studies have already established clearly two facts:

- Gadolinium residues are actually accumulating in the brains of patients who undergo multiple contrast MR exams (both brain and non-brain) during the course of their lifetime.
- Less-stable chelates are much more prone than stable agents to lead to long-term Gadolinium depositions in the brain. These residues were seen post-mortem under T1 hyper signal in patient studies.

IMAGING COMMUNITY AWAITING A VERDICT ON A POTENTIALLY HARMFUL EFFECT OF BRAIN RESIDUES

While clinical studies have not yet established the harmful effect of the accumulation of brain residues, they are raising eyebrows in the medical imaging community. What if the more than 100 million doses of GBCA-enhanced MR procedures performed over the past 25 years are actually harmful to patients?

At a time when radiation dose safety, notably from Computed Tomography (CT) imaging, is the safety concern stealing most of the attention, other modalities are being scrutinized as well. In this specific case, a growing concern for patients who undergo a large number of MRI exams. Multiple-sclerosis patients would be one example of the most vulnerable populations.

SEVEN PRODUCTS UNDER FOUR PRODUCT CATEGORIES

While a careful wait-and-see attitude seems to prevail right now in the imaging community, the ongoing developments are bringing the strength and stability of commercially available GBCA chelates to the forefront of current discussions. Two attributes are used to classify each GBCA product into four product categories with varying levels of strength and stability: Linear (Open Chain) versus Non-Linear (or Macrocyclic or Closed Chain) GBCAs and Ionic versus Non-Ionic GBCAs.

Of the four categories, macrocyclic ionic is the most stable; they have the strongest ligand complexes for a chelate, which translates into better fixation or enclosure of Gadolinium.

FIGURE 1

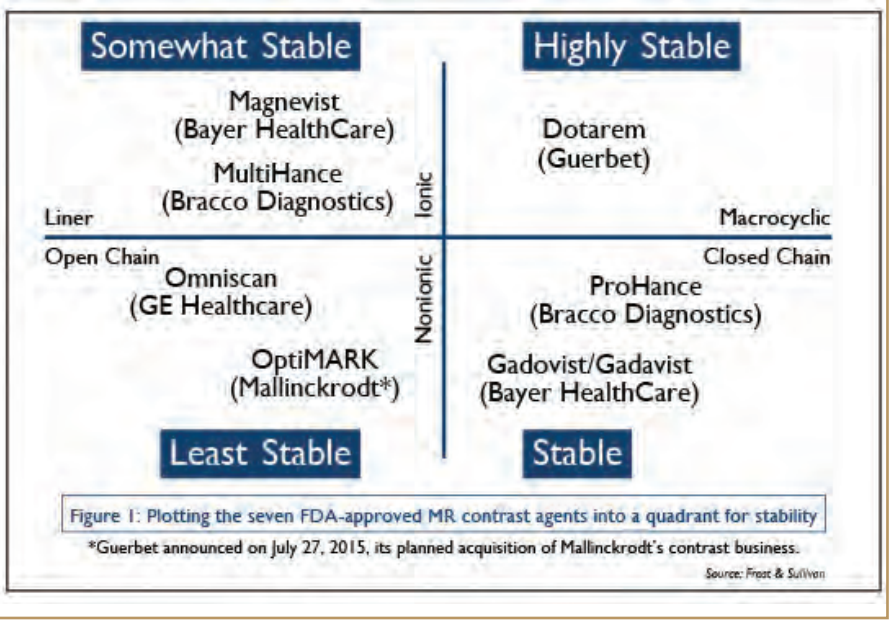

Figure 1: Plotting the seven FDA-approved MR contrast agents into a quadrant for stability

*Guerbet announced on July 27, 2015, its planned acquisition of Mallinckrodt's contrast business.

Source: Frost & Sullivan

A CATCH 22 SITUATION THAT MAY GIVE RISE TO NEW COMPETITIVE DYNAMICS

The confluence of two major elements is putting the market for GBCAs in a typical catch 22 situation, which may be hinting at an imminent shake-up in the competitive landscape:

- The GBCA market is largely price-driven; it is highly influenced by group purchasing organizations (GPOs) having long-established, high-volume, and heavily negotiated contracts with providers.

- The less-stable chelate products on the market are the least expensive, as well as the ones with the largest market share. Conversely, more stable chelate products carry a slightly higher price tag and have a much smaller market share today.

IN THE MIDST OF UNCERTAINTY, BIG QUESTIONS ARISING

Some of the big questions in the current context are: Will the market react to these initial clinical research findings by shifting toward more stable products, regardless of price differentials? Would a market shift start to occur even before the risk posed by Gadolinium brain depositions is clearly determined through potentially upcoming studies? Are we facing a similar scenario as in 2006, or will any potentially upcoming regulatory measures distinguish between individual MR contrast products this time? If that is the case, will radiologists need to take more ownership of patient referrals to contrast-enhanced MR procedures? If radiologists are to be responsible, how will legislators deal with their concerns regarding the Stark Amendment Law, which is making them shy away from getting too closely involved from imaging orders? That is the one golden question that Kanal and Tweedle raised in their recent and highly controversial article published in Radiology. ◆

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHY

Nadim Michel Daher is a Principal Analyst with Frost & Sullivan's Advanced Medical Technologies practice, specializing in medical imaging informatics and modalities. With almost a decade of industry expertise covering North American and Middle Eastern markets, his knowledge base covers radiology, PACS/RIS, advanced visualization, IT middeware, teleradiology, as well as CT, MRI, and ultrasound technologies. He earned his MS in Biomedical Engineering from the University of Southern California.

DRUG DEVELOPMENT

Don't Overlook Key Preclinical Research

By: Robert Wenslow, PhD, and Ann Newman, PhD

INTRODUCTION

Critical factors impacting drug delivery, such as the overall pharmacokinetics profile (PK) and the pharmacodynamics profile (PD) of the compound, are often impacted by solubility, dissolution rate, and dissolution location of the drug once it is administered, especially for oral medications.

Animal-based toxicology studies are a pivotal part of any drug development program in which the drug is typically administered orally. The goal for any drug development team is to test and validate options that will provide optimal administration and uptake, and to identify dose-limiting toxicity levels.

However, in a rush to initiate such animal-based toxicity testing, many drug development teams skip key laboratory-based testing, simulation, and modeling options. This results in missed opportunities to thoroughly characterize the crucial solid-state materials properties that will impact the behavior and performance of the active pharmaceutical ingredient (API).

Because characteristics such as crystal form, size, surface area, and more (Figure 1) have a direct impact on the most appropriate and advantageous form of the API, it is in the drug discovery team's best interest to partner with material scientists and formulation experts earlier in the process, to develop the needed insight earlier — before animal-based testing is initiated. Such an approach allows the team to quickly identify the most relevant solubility (kinetic and equilibrium), bioavailability, and toxicology values that are needed to accurately demonstrate the drug's capabilities and initiate human-based clinical trials.

Too often, a trial-and-error approach is used, especially by smaller biopharmaceutical companies, which may lack the necessary internal resources or expertise (Figure 2). However, when disappointing early testing does not yield the anticipated results, the team invariably ends up going back to the drawing board, to carry out a series of iterative changes (for instance, altering the API phase or its polymorph, or varying the formulation) in an effort to achieve better test data. Such late changes typically require additional or different toxicity and efficacy studies to be carried out, which drives up costs and adds complexity and risk to the process.

The following discusses an approach that can help the team develop greater depth of knowledge earlier in the process, and use it to realize shorter overall timelines, and reduced risk and cost. When smaller biotechnology companies do not have the required solid-state research capabilities in house, they should consider partnering with a contract research organization (CRO) that has broad and deep drug discovery and drug development knowledge and expertise, particularly with regard to solid-form selection and screening, toxicology formulation screening, excipient selection, and more.

FORM & FUNCTION

Most APIs can be produced in a variety of solid forms (ie, as a salt, a co-crystal, in free form, as a solvate or hydrate, in anhydrous free forms, in metastable forms, or as a polymorph, Figure 3). The specific API form may have a direct impact on animal-based toxicology testing results, and on other later drug-development, scale-up, and production pathways.

In most toxicology studies, the drug is administered as a solution or suspension. Nonetheless, it is the nature of the solid API itself that dictates the nature of the solution being prepared

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for testing (in terms of how much of the drug can be dissolved to reach the maximum dose, how much of the drug will stay in solution or remain in a suspension solution, and so on). For example, unwanted precipitation of the API would change the absorption, bioavailability, and pharmacokinetic characteristics of the candidate drug thereby significantly altering the preliminary testing data.

When rigorous lab-based testing, modeling, simulation, and analysis is used to better characterize the pharmacokinetic properties of the investigational drug, the team is able to more accurately predict and validate bioavailability and the concentration of the drug in the blood or urine over time during animal-based toxicity testing (that is, the PK profile). This helps the researchers to isolate and reduce avoidable variability earlier in the process, so that the actual testing data truly reflect the inherent variability of the compound itself, in terms of metabolism, excretion, and so on — not just variability that may be the attributable to too many other "moving parts."

FOCUSING THE EFFORT EARLY

The behavior of the solubilized API will vary with the exact nature of its liquid-based formulation. To minimize the impact of such variation, the drug development team must carry out sufficient lab-based testing to accurately characterize the conditions at which the concentration of the API will change over time (for instance, precipitating out of solution), and to anticipate how the precise formulation will function in the gastrointestinal tract. To do this, lab-based screening techniques should be used to evaluate solubility/dissolution rates and possible precipitation of the competing candidate compounds in the face of simulated gastric fluids and simulated intestinal fluids.

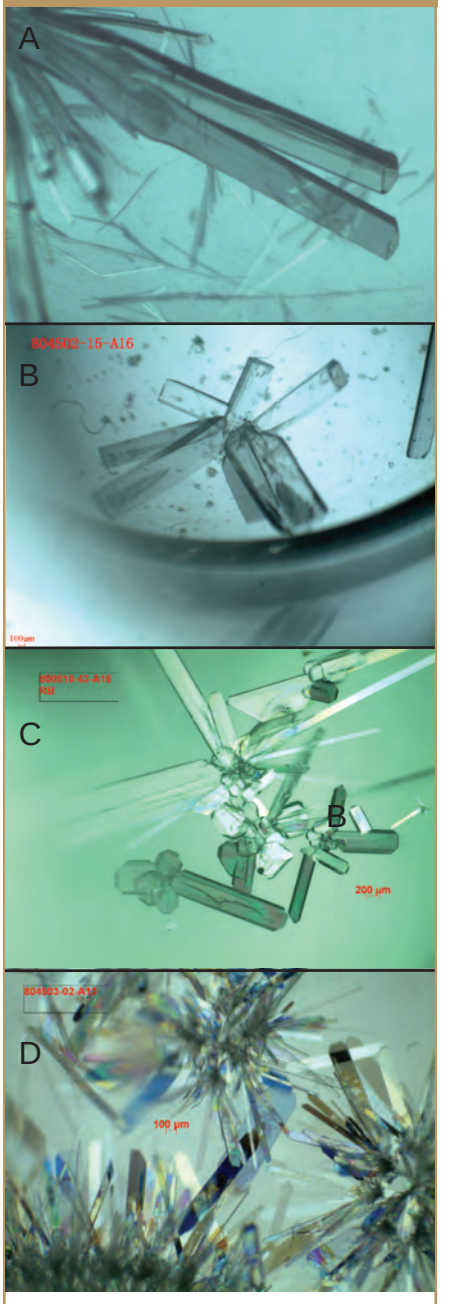
Similarly, both conventional and non-conventional formulation options (for instance, using a spray-dried dispersion formulation) should be considered prior to the initiation of animal-based testing. The goal is to rule out sub-optimal options and hone in on the most-promising forms and formulations as the process moves forward into the toxicology-testing phase.

Ideally, early preclinical drug development efforts should incorporate the following types of solid-state research:

- Polymorph/salt/co-crystal screening
- Non-conventional formulation screening
- Thermodynamic form relationship
- Solid-form selection
- Single-crystal growth (to produce individual crystals that are acceptable for single crystal x-ray diffraction (SCXRD) structure determination)

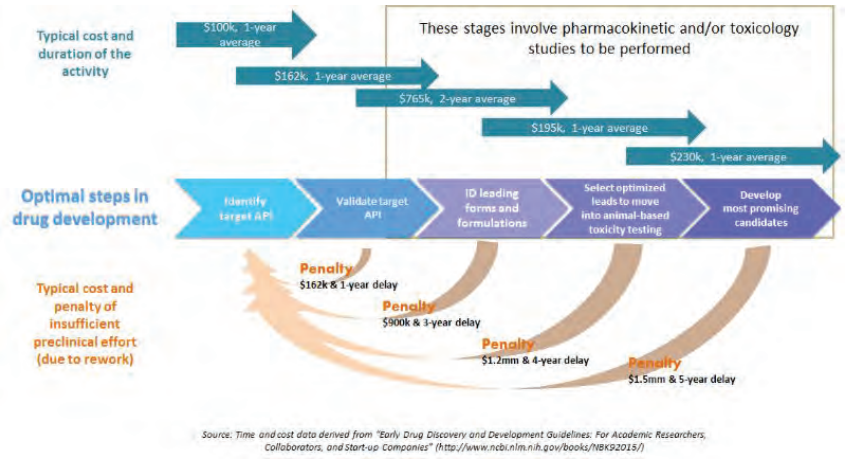
Similarly, various options that are available to enhance the solubility of the API in solution should also be investigated. The goal is to develop a rational framework to do the right type of testing at the right time for the project at hand, in order to avoid missed opportunities and reduce excessive or

FIGURE 1A-D



The ability to consistently produce the API — in terms of the desired crystal form, and repeatable crystal with desired morphology and purity — can have a direct impact on drug product properties, specifically bioavailability and stability. Efforts to understand and control material properties early in the process can help to reduce trial-and-error once animal-based trials get underway. (Source: Crystal Pharmatech)

FIGURE 2



Too often, drug developers are anxious to move the process forward. However, without sufficient preclinical work, a rush to initiate animal-base trials often yields disappointing results, with a range of demonstrable cost and timeline impacts. (Source: Crystal Pharmatech)

irrelevant effort (this is discussed in greater detail later).

When material characteristics (and hence behavioral characteristics in the human body) are not thoroughly investigated and characterized early enough in the process, the initial animal-based toxicity testing can produce "muddy data." Such data suggests confusing or disappointing results that don't accurately reflect the actual capabilities of the API, but rather diverge greatly from what was expected on a dose-proportional basis. Such testing data may appear erratic, but in truth, the variability stems from the form or formulation being administered, and is not necessarily a reflection of the efficacy or toxicity of the API or compound itself.

If the investigational compound shows poor exposure during initial animal-based toxicology testing, the team will want to understand the mechanism that is to blame. Common factors to be considered include the following:

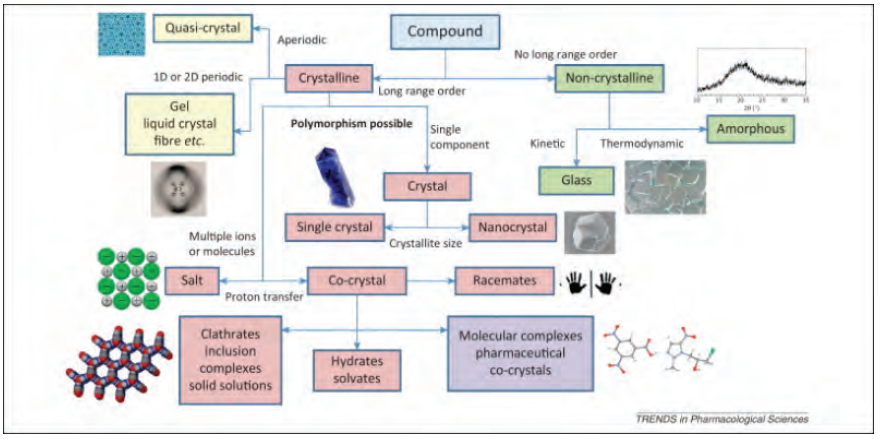
- Poor permeability/efflux, molecular weight, charge, other factors
- Fast metabolic degradation/first-pass
- Chemical or physical instability
- Poor solubility
- Inappropriate formulations (for instance, amorphous, nano, or cosolvent, or non-aqueous solutions)
- Particle size
- Crystal form
- Other

THE BUSINESS CASE

Any efforts to improve the preclinical development through better material science research will have direct and strategic business implications, with return on investment coming from the ability to:

- Shorten timelines (and therefore potentially shorten the time to market)
- Maximize earnings potential, revenue, profit margin, and

FIGURE 3



Most APIs can be produced in a variety of solid forms all of which can impact testing results, as well as critical decisions related to drug development, scale-up, and commercial production. Proper use of rigorous, lab-based testing, modeling, simulation, and analysis can yield fewer surprises during all of these processes. (Source: Steed, Jonathan W. The role of co-crystals in pharmaceutical design, Trends in Pharamacological Sciences.2013;34(3):185-193. reprinted with permission)

"The behavior of solubilized API will vary with the exact nature of its liquid-based formulation. To minimize the impact of such variation, the drug development team must carry out sufficient lab-based testing to accurately characterize the conditions at which the concentration of the API will change over time (for instance, precipitating out of solution), and to anticipate how the precise formulation will function in the gastrointestinal tract."

market share (by receiving regulatory approval sooner)

- Minimize competition in some cases (through market exclusivity and other benefits if the product is first to market for a given indication)
- Eliminate unnecessary experiments and PK studies
- Reduce the number of animals required for toxicology studies
- Reduce overall risk associated with the program

And importantly, robust preclinical drug development efforts have the potential to strengthen the overall value of the drug portfolio for potential partnership or acquisition opportunities — from a due diligence perspective — by reducing risk, developing more-robust data, and potentially shortening the overall regulatory and commercialization pathway.

USE A RIGOROUS METHODOLOGY

The goal is to not just throw every tool at the problem, but rather to use a rational approach — using lab-based techniques (Figure 4), modeling, and analysis, well ahead of the onset of animal-based testing — to better understand the fundamentals of what is going on in your system. The following types of questions should be used to guide the effort:

- What is the ideal dose in solution?
- What is the ideal API form?
- Does particle size impact exposure?
- What is the ideal vehicle to use to produce the desired formulation?
- What happens when this solution

FIGURE 4

The goal of a sound program is to use minimally invasive, in vitro, bench-top testing techniques in the most strategic way to mimic the anticipated conditions. This can improve toxicity testing results, limit the number of animals required for testing, and streamline the overall drug development program. (Source: Crystal Pharmatech)

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encounters the anticipated pH that is representative of the conditions in the animal's gastrointestinal system?

- Will the solution become gelatinous?
- Will the active ingredients come out of solution?
- Is the proposed solution able to meet the maximum required dose with no problems (physical, toxicological, or other)?
- Does the delivery vehicle itself present any safety concerns?
- Are preparation methods scalable?
- Can dose-limiting toxicity be predicted (and then verified during toxicity testing)?

The ability to understand the basics early on — using minimally invasive, in vitro, bench-top testing techniques to mimic the anticipated conditions — can improve toxicity testing results, and importantly, can help to greatly limit the number of animals required for testing. The steps discussed briefly below provide a roadmap for carrying out pre-clinical, drug-screening and drug-formulation efforts:

1. **Generate & Identify Candidate Compounds**: characterize promising leads and develop small-scale scale-up routes
2. **Phase Characterization:** Evaluate API phase options and solubility profiles
3. **Phase Evaluation:** Evaluate stability and bioavailability of the candidate compounds
4. **Phase Selection:** Start making decisions about scale-up, formulation considerations and process control aspects

In an effort to save time and money, and start generating data, most of today's drug development teams skip past Steps 2, 3, and 4, jumping right from Step 1 to the initiation of animal-based toxicology studies. As noted earlier, investments of time and effort made during Steps 2, 3, and 4 are well spent, providing the biggest possibility of payback over the long run. ◆

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Dr. Robert Wenslow is Vice-President of Business Development at Crystal Pharmatech. He is a seasoned drug development scientist with a strong background in pharmaceutical characterization. He has extensive experience in all solid-state research issues relating to the pharmaceutical industry. Prior to founding Crystal Pharmatech, Dr. Wenslow spent 14 years at Merck & Co. His group at Merck supported, on average, 30 drug development projects per year. He also spent 2 years at Merck's manufacturing site in Ballydine, Ireland, where he was responsible for creating and leading the first research-based Analytical Science Group in the Merck Manufacturing Network. Dr. Wenslow earned his PhD in Analytical Chemistry from Pennsylvania State University. He has presented papers at 10 professional conferences and published more than 25 peer-reviewed journal articles. He is also co-author on more than 10 patents. He can be reached at Robert_Wenslow@crystalpharmatech.com.

Dr. Ann Newman is Vice-President of Scientific Development and Head of the Scientific Advisory Board at Crystal Pharmatech, and pharmaceutical consultant at Seventh Street Development Group. She has more than 20 years of large pharma and contract research experience. For 10 years, Dr. Newman performed characterization studies on a wide range of pharmaceutical studies at Bristol-Myers Squibb, covering drug substance and product scale-up, from late drug discovery to launch and manufacturing. She has also held key roles at SSCI, Inc. and Aptuit, and holds an adjunct faculty in Industrial and Physical Pharmacy at Purdue University. She earned her PhD in Chemistry from the University of Connecticut, and is the author or collaborator on more than 45 publications, 90 technical presentations, and 55 webinars. She can be reached at ann@seventhstreetdev.com.

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External Delivery

It's Never Too Late

By: John A. Bermingham

John A. Bermingham is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America.

"You're going to do what?" was my wife's reaction to my announcement."Come on, you know it is something I've always wanted to do," was my response. "Don't you think that you're a little old for this?" she fired back. "It's never too late," I countered.

What she and I were talking about was my decision to go back to college to earn my MBA. The reason I am doing this is because I want to teach at the college level when I make the decision to call corporate life quits. I am aiming for a good business school, but a roadblock for me is that I cannot teach at the college level without a graduate degree. So with some apprehension, I met with an advisor at Centenary College here in New Jersey and signed up. I chose Centenary College for three reasons:

1. My son is a professor at Centenary

2. They have what is considered one of the best online MBA programs taught by professors who are at the top of their game

3. They gave me a substantial tuition discount because I am a veteran.

When hearing about my return to academia, a lot of my friends reacted with smiles and gave me positive reinforcement. But I know what they were really thinking was that I was following in Rodney Dangerfield's footsteps if you remember his movie, *Back to School*.

Actually, I have found that my fellow students are very accepting to my participation in the MBA program. I hadn't expected that being that my 5 children are all older than most of my fellow students. One thing however has stood out during the first year of my pursuit.

When I announced I was returning to college to earn my MBA, there were a lot of comments from people to me saying that this should be a slam-dunk for me with all of my business experience. That turned out to be very incorrect. It has been almost 30 years since I went to Business School, and the business world has changed dramatically. I have learned many new ideas and ways of thinking about business than I had done previously. From Leadership, to Managerial Economics, to Marketing, to IT, the world has changed and changed in a big way. Running a company with 1980s methods will not work today.

The culprit is the Internet. This technology has changed the world forever, and today's captains of industry had best understand how to leverage it against competition and what competition can do against you using the Internet.

I highly recommend that if you have been away from school for a decade or two, you might consider an online MBA or at least a few online courses to get yourself tuned up. I will tell you that going back to school late in life is a great experience. You are much more focused and appreciate the education in a way you never have before. It is challenging from an academic perspective, and yet, the material is understandable and holds your interest. See, an old dog can learn new tricks. ◆

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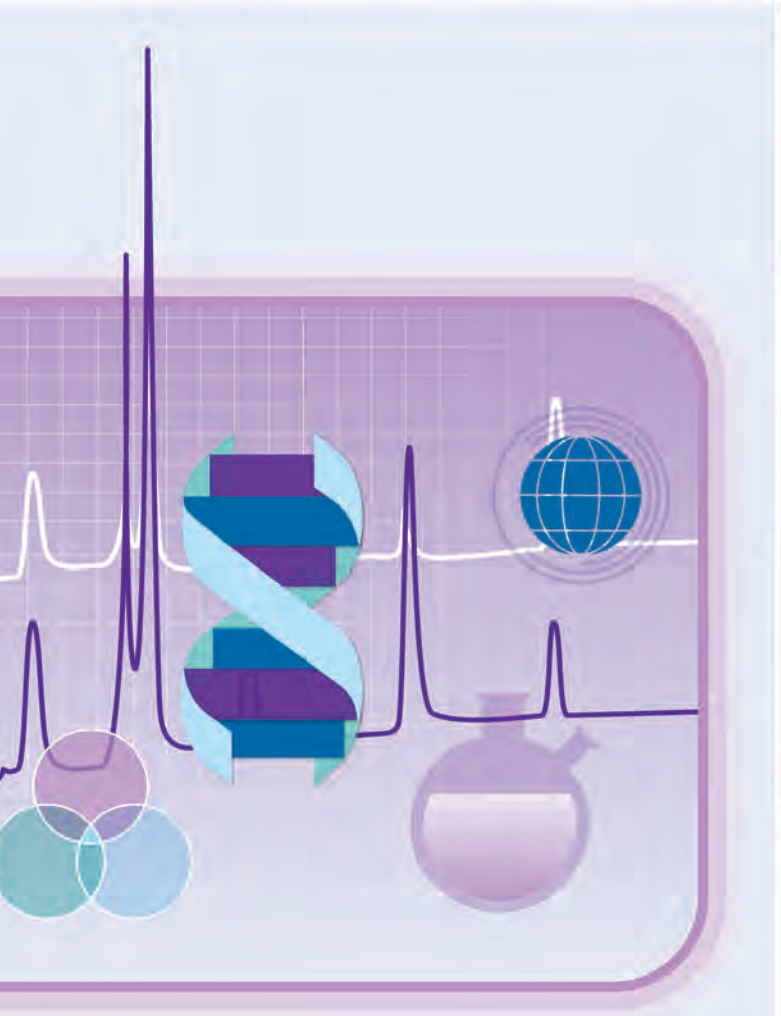

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