Drug Development & Delivery

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

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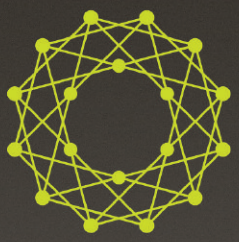

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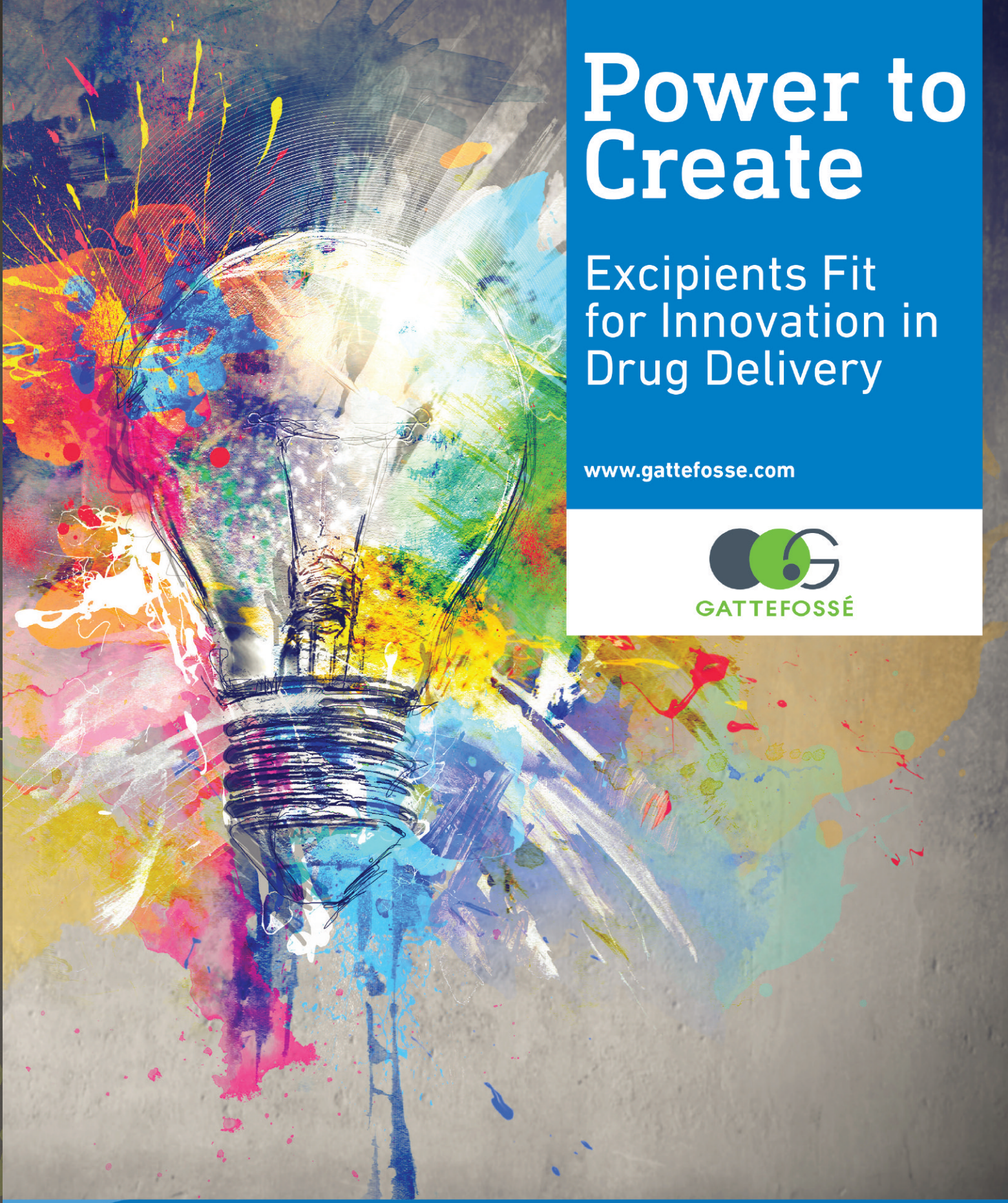

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"Improving productivity in pharmaceutical development is important but shouldn't come at the expense of creativity. To develop truly innovative products, R&D relies on pharmaceutical developers thinking outside the box. Only with creative people willing to take responsibility for new ideas will we be able to meet the evolving needs of 21st-Century patients and consumers."

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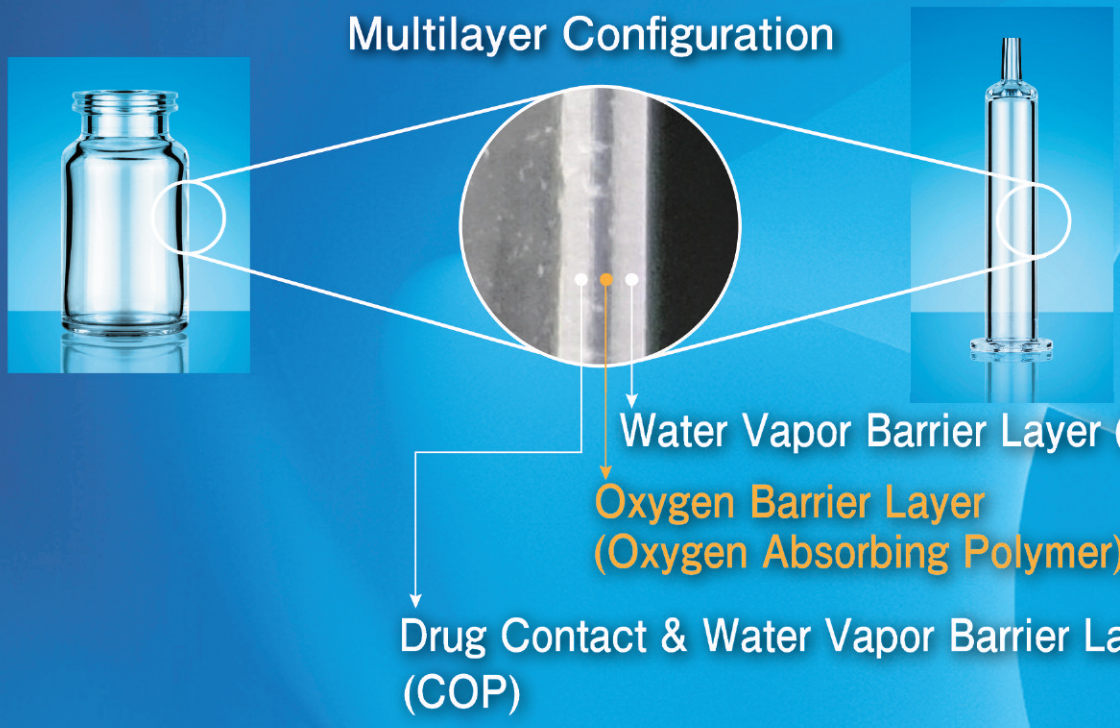

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Bioasis & WuXi Biologics Announce Initial Strategic Development & Manufacturing Collaboration

Bioasis Technologies, Inc. and Wuxi Biologics recently announced an initial strategic collaboration for the development and manufacturing of xB3-001, Bioasis' lead investigational biological candidate to treat brain cancer.

Bioasis is a biopharmaceutical company developing xB3, a proprietary platform technology for the delivery of therapeutics across the blood-brain barrier (BBB) and the treatment of CNS disorders in areas of high unmet medical-need, including brain cancers and neurodegenerative diseases.

Headquartered in Wuxi city, Jiangsu province, China, WuXi Biologics is a leading global platform company providing end-to-end solutions for biologics with a mission to accelerate and transform biologics discovery, development, and manufacturing to benefit patients around the world.

"The initiation of manufacturing for xB3-001 is a pivotal milestone for Bioasis as we look to advance our lead program in HER2+ breast cancer brain metastases," said Mark Day, PhD, President and Chief Executive Officer, Bioasis. "WuXi Biologics' expertise and experience in manufacturing biologics is instrumental to Bioasis in developing our pipeline."

The delivery of most biologics across the BBB and into the brain has been the single greatest challenge to treating brain diseases. Bioasis is engineering its first biologic product candidate, xB3-001, to overcome this obstacle in brain cancer. Manufacturing these sophisticated therapies requires a tailor-made approach, with expertise and agility in cell line, process and formulation development.

"We are excited to take on this work with Bioasis to enable them bringing innovative therapies to patients suffering from brain cancer," said Dr. Chris Chen, chief executive officer, WuXi Biologics. "This collaboration allows us to leverage our expertise across biological drug development and anticipate Bioasis' needs as they move from pre-clinical to clinical and beyond."

Through this partnership Bioasis will have access to WuXi Biologics' extensive expertise and technologies from cell line construction and development, cell culture process development, purification process development and formulation development. WuXi Biologics will focus on ensuring that Bioasis' drug product candidates are manufactured with optimal formulation, stability and exceptional quality for the clinic.

WuXi Biologics, a Hong Kong-listed company, is the only open-access biologics technology platform in the world offering end-to-end solutions to empower organizations to discover, develop, and manufacture biologics from concept to commercial manufacturing. Our company history and achievements demonstrate our commitment to providing a truly ONE-stop service offering and value proposition to our global clients. For more information on WuXi Biologics, visit www.wuxibiologics.com.

Bioasis Technologies Inc. is a biopharmaceutical company developing xB3, a proprietary platform technology for the delivery of therapeutics across the blood-brain barrier (BBB) and the treatment of CNS disorders, including brain cancers and neurodegenerative diseases. The delivery of therapeutics across the BBB represents the final frontier in treating neurological disorders. The in-house development programs at Bioasis are designed to develop symptomatic and disease-modifying treatments for brain-related diseases and disorders. The company maintains headquarters in Richmond, BC, Canada, with offices in Guilford, CT.

BC Platforms Partners With Google Cloud to Offer Transformational & Scalable Genomic Solutions Worldwide

BC Platforms recently announced it has partnered with Google Cloud to deliver its highly scalable integrated genomics and clinical data solutions to hospital and industry partners worldwide. In addition to storage, archiving, and calculation capacity, Google Cloud genomics and AI tools, including DeepVariant, will be supported.

BC Platforms offers a unique technology capable of processing thousands of genomes per day, produced using either genotype arrays or next-generation sequencing. The introduction of BC Platform's capabilities on Google Cloud will enable better access for pharmaceutical companies to identify biobank data sources across the globe for research and development. With BC Platforms on Google Cloud, healthcare institutions wishing to deliver on the promise of precision medicine on population scale will be able to provide cost-effective and actionable patient reports based on genotype array or NGS data.

"We are excited to collaborate with BC Platforms to provide their highly scalable and fully integrated service offering in Google Cloud. We expect the integration of our technology capabilities to facilitate the adoption of genomics both in clinical and research settings," said Jonathan Sheffi, Product Manager for Biomedical Data at Google Cloud.

Tero Silvola, CEO of BC Platforms, added "We are delighted to be partnering with Google Cloud to expand our genomic and clinical data offering in the Google Cloud ecosystem. We are committed to providing highly scalable and integrated solutions to our customers and partners. Our goal is to transform the future of research and clinical practice worldwide in order to drive precision medicine on a population scale."

BC Platforms is a world leader in providing powerful genomic data management and analysis solutions. Our high performing genomic data management platform enables flexible data integration, secure analysis and interpretation of molecular and clinical information. The company has launched and opened a global network of biobanks, known as BCRQUEST.COM, to provide genomic and clinical cohort data for pharmaceutical and medical research and development. BC Platforms' vision is to build the world's leading analytics platform for healthcare and industry by 2020, providing access to diverse genomic and clinical data and samples from more than 5 million subjects consolidated from a global network of biobanks.

Founded in 1997 from an MIT Whitehead project spinoff, the Company has a strong scientific heritage underpinned by 20 years of working in close collaboration with a network of leading researchers, developers, manufacturers and vendors. BC Platforms has global operations with its headquarters in Basel, Switzerland, research and development in Helsinki, Finland, and sales and marketing in London, Boston, and Vancouver. For more information, visit www.bcplatforms.com.

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Catalent Biologics & Valerius Biopharma to Collaborate on Specialty Biosimilars

Catalent Pharma Solutions and Valerius Biopharma AG recently announced that they are to collaborate on the development and manufacture of Valerius' biosimilar products.

Under the agreement, Catalent Biologics will provide cell line development and support cGMP manufacturing activities from Phase I through to commercial stages at its state-of-the-art biologics manufacturing facility in Madison, Wisconsin.

The project will utilize Catalent's proprietary GPEx technology, which creates high-performance, highly stable production cell lines in a wide variety of mammalian host cells. To date, over 460 different monoclonal antibodies and monoclonal antibody fusions, and over 50 different recombinant proteins have been produced using the GPEx system, achieving large scale fed-batch production titers of over 7 g/L. The advantages of applying GPEx technology span from early feasibility studies, to clinical manufacturing, to commercial-scale production.

Valerius Biopharma AG is a biopharmaceutical company founded to develop biosimilar products as alternatives to high-priced biologics, for indications where there is a substantial medical need. The company has built a research and development hub of scientists and experts with decades of experience in the development of biopharmaceutical and biosimilar compounds, as well as profound clinical and regulatory expertise. The company's current product pipeline comprises four biosimilar products in different development stages.

"Our business mission is to make the treatment of severe, life-threatening and rare diseases more affordable for patients worldwide by developing biosimilars that meet the highest regulatory standards," said Andreas Herrmann, CEO of Valerius. He added, "We selected Catalent as our development and manufacturing partner because of their technical knowledge and expertise in the cGMP manufacture of biosimilars, and proven track record in bringing innovative treatments to market."

Mike Riley, Vice President and General Manager of Drug Substance and Bioanalytical Services, Catalent Biologics, added "We are pleased to partner with Valerius on their biologic-based therapeutics for many important indications. We look forward to supporting them in their goal of producing affordable biosimilars that will provide more equal access to medicinal products."

Opened in April 2013 and recently expanded, Catalent Biologics' Madison site provides development, manufacturing and analytical services for new biological entities and biosimilars. The facility was designed for flexible cGMP production from 10 liters up to 4,000-liter scale, and non-GMP production up to 250-liter scale and makes extensive use of single-use technologies and unidirectional flow to maximize safety and efficiency. Manufacturing is supported by integrated analytical, process and formulation development capabilities and separate microbiology and quality control functions.

Valerius Biopharma AG is a Swiss biopharmaceutical company that has been founded to provide interchangeable treatment options for high-priced biologics, by developing specialty biosimilars for therapeutic indications with high medical need. Catalent is the leading global provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products.

Saama Technologies & ICON Commercialization & Outcomes Partner to Unlock the Value of Real World Evidence

Saama Technologies and ICON plc have recently partnered to accelerate the use of Real World Evidence (RWE) across the product lifecycle and drive mission critical decisions for medical affairs, reimbursement and commercialization functions.

Biopharmaceutical, medical device, and diagnostic companies are seeking comprehensive RWE technology solutions that can support an array of RWE applications across the enterprise. Through this partnership, ICON brings real world data (RWD) strategy and platform deployment expertise to complement Saama's deep experience in utilizing innovative applications, such as Natural Language Processing, Machine Learning and advanced Data Visualization tools.

The volume of healthcare data continues to grow exponentially and is forecasted to hit more than two zettabytes by 2020. This dramatic increase in the availability of and access to anonymized electronic patient records requires new approaches for closing the medical product development and commercialization cycle.

"Saama is very excited about our partnership with ICON, which further expands our new Life Science Ecosystem," said Murali Krishnam, VP Strategic Partnerships and Alliances of Saama. "Saama's Artificial Intelligence-based analytics platform, combined with ICON's Real World Evidence, Strategy, and Analytic (RWESA) services, will help biopharmaceutical, medical device, and diagnostics companies rapidly deploy a RWE-generating platform. This will support greater efficiencies in drug development, providing the RWE needed to inform medical affairs, regulatory and reimbursement decisions and underscoring the value of the medical technology to patients and providers."

"Our partnership with Saama will help us to unlock the real world data for our sponsors, offering improved clarity regarding the various types of real world data and how they can best generate RWE to inform clinical and commercialization strategies," said Ramita Tandon, Executive Vice President of ICON's Commercialization and Outcomes Division.

Saama's award-winning Life Science Analytics Cloud (LSAC) integrates multiple sources of structured, unstructured and real-time data to optimize clinical and commercialization processes for deployment in less than 90 days, thus securing better business outcomes faster. In addition, LSAC further lowers the total cost of platform ownership significantly for continuous RWE generation and for managing evolving business needs. This approach integrates seamlessly with ICON's unique Real World Intelligence approach to combine RWD and advanced expertise in answering important questions on patient experience, market access requirements, strategic evidence planning and roadmap development.

Through this partnership, ICON becomes part of Saama's recently announced Life Science Ecosystem, which combines the unparalleled benefits of Saama's Life Science Analytics Cloud with the specific strengths of clinical or real-world data providers. For information about joining Saama's Life Science Ecosystem, or to schedule a demonstration of Saama and ICON's RWE data analytics solutions, visit http://www.saama.com/.

Saama Technologies is the advanced data and analytics company delivering actionable business insights for life sciences and the Global 2000. ICON plc is a global provider of outsourced drug development and commercialisation solutions and services to pharmaceutical, biotechnology, medical device, and government and public health organisations.

Soleno Therapeutics Announces Initiation of Phase III Clinical Trial

Soleno Therapeutics, Inc. recently announced it has initiated its multi-center Phase III clinical trial of Diazoxide Choline Controlled-Release (DCCR) for the treatment of Prader-Willi Syndrome (PWS). Seattle Children's Hospital is the first site to be activated and Parisa Salehi, MD, is the Principal Investigator for the trial at this site.

"Prader-Willi Syndrome leads to hyperphagia that can cause life-threatening obesity if left uncontrolled," said Dr. Salehi. "This excessive hunger can cause significant harm to the lives of these individuals and their families. There is a lack of effective medical therapy targeting hunger in this population, and such a drug would be life-altering. Based on the data generated to date, DCCR has the potential to address this treatment void. We look forward to further evaluating DCCR in this important Phase III trial."

"The initiation of the Phase III clinical trial of DCCR for the treatment of PWS represents a significant milestone for Soleno," said Anish Bhatnagar, M.D., Chief Executive Officer of Soleno. "Importantly, following meetings with the U.S. Food and Drug Administration, we have alignment with the agency on the key aspects of the Phase III clinical trial. We look forward to working with our clinical trial sites and the PWS community to successfully complete the trial."

The Phase III clinical trial is a multi-center, randomized, double-blind, placebo-controlled study for DCCR that will treat approximately 100 PWS patients at 10-15 sites in the U.S. This trial is anticipated to take approximately 9-12 months to complete. DCCR has orphan designation for the treatment of PWS in the US and in the EU.

Diazoxide choline controlled-release tablet is a novel, proprietary extended-release, crystalline salt formulation of diazoxide, which is administered once-daily. The parent molecule, diazoxide, has been used for decades in thousands of patients in a few rare diseases in neonates, infants, children and adults, but has not been approved for use in PWS. Soleno conceived of and established extensive patent protection on the therapeutic use of diazoxide and DCCR in patients with PWS. The DCCR development program is supported by positive data from five completed Phase I clinical studies in various metabolic indications or in healthy volunteers and three completed Phase II clinical studies, one of which was in PWS patients. In the PWS Phase II study, DCCR showed promise in addressing hyperphagia, the hallmark symptoms of PWS.

Soleno is focused on the development and commercialization of novel therapeutics for the treatment of rare diseases. The company is currently advancing its lead candidate, DCCR, a once-daily oral tablet for the treatment of PWS, into a Phase III clinical development program in early 2018. For more information, please visit www.soleno.life.

Bellerophon Reaches Agreement With FDA on Study Design of Phase 2b Trial

Bellerophon Therapeutics, Inc. recently announced that, following the receipt of minutes from a recent meeting with the US FDA, the company has reached agreement with the FDA on all key aspects of its planned Phase 2b study of INOpulse for the treatment of Pulmonary Hypertension Associated with Chronic Obstructive Pulmonary Disease (PH-COPD).

The US-based Phase 2b study will be a double-blind, placebo-controlled, clinical trial in approximately 90 PH-COPD patients assessing the benefit of pulsed inhaled nitric oxide (iNO) delivered by the INOpulse system. The primary end point will be 6-minute walking distance (6MWD), and the study will also assess multiple secondary endpoints including right ventricular function.

"Reaching agreement with the FDA on the Phase 2b study design in PH-COPD represents an important achievement for our INOpulse development program," said Fabian Tenenbaum, Chief Executive Officer of Bellerophon. "Based on the data generated to date and INOpulse's dual mechanism of action, to provide targeted vasodilation as well as improve ventilation-perfusion matching, we believe INOpulse has the potential to be the first treatment approved for PH-COPD, and we look forward to advancing our INOpulse therapy in this serious and unmet medical condition."

The FDA meeting followed positive Phase 2a data, reported in September 2017 that showed statistically significant and clinically meaningful increases in 6MWD after both 2 and 4 weeks of treatment on INOpulse (+50.7m; p=0.04), as compared to baseline. In addition, the trial results demonstrated a statistically significant increase (average 4.2%; p=0.03) in blood vessel volume and a statistically significant correlation in Ventilation-Vasodilation (p=0.01), indicating targeted delivery to the well-ventilated alveoli, as well as clinically meaningful decrease of 19.9% (p=0.02) in systolic pulmonary arterial pressure. The therapy was well-tolerated with no related safety concerns.

COPD is a common, but potentially life-altering disease with a diagnosed prevalence greater than 12 million in the US. Approximately 25%-30% of COPD patients have associated pulmonary hypertension. Although there are multiple therapies indicated for the treatment of COPD, there are no approved therapies for the treatment of PH associated with COPD.

Bellerophon Therapeutics is a clinical-stage biotherapeutics company focused on developing innovative therapies at the intersection of drugs and devices that address significant unmet medical needs in the treatment of cardiopulmonary diseases. The company is currently developing three product candidates under its INOpulse program, a proprietary pulsatile nitric oxide delivery system. The first is for the treatment of PAH, for which the company has commenced Phase 3 clinical trials. The second is for the treatment of pulmonary hypertension associated with chronic obstructive pulmonary disease (PH-COPD) and the third candidate is for the treatment of pulmonary hypertension associated with Interstitial Lung Disease (PH-ILD), both of which are in Phase 2 development. For more information, visit www.bellerophon.com.

NanoBio Announces Corporate Name Change to BlueWillow Biologics & Closes $10-Million Financing

NanoBio Corporation recently announced it has changed its corporate name to BlueWillow Biologics in conjunction with the closing of a $10-million Series A financing. The company's new name reflects its evolution to a vaccines-focused company and commitment to advancing its novel intranasal technology to develop new vaccines for several respiratory and sexually transmitted diseases.

The Series A financing round was led by North Coast Technology Investors, Line Moon Ventures, and the University of Michigan through its MINTS initiative.

The company was originally founded as NanoBio Corporation to develop topical nanoscale therapies for various dermatology applications. BlueWillow will continue to develop skin and wound treatments through partnerships and external collaborations under the NanoBio trademark.

BlueWillow's innovative intranasal vaccine platform is built upon the company's patented NanoVax technology that employs a unique oil-in-water nanoemulsion adjuvant to elicit both systemic and mucosal immunity. Most infectious pathogens enter the body across mucosal surfaces, yet most vaccines today are injected and fail to elicit mucosal immunity. BlueWillow's technology has the potential to improve upon many existing vaccines as well as enable the creation of new vaccines for diseases that currently cannot be prevented through vaccination.

"Over the past several years, our research has increasingly demonstrated that our intranasal platform can play a pivotal role in the vaccines of tomorrow," said Dave Peralta, Chief Executive Officer of BlueWillow. "Much of our data points to increased protection against some of the world's most severe respiratory and sexually transmitted infections. With the commitment of our Series A investors and the tremendous support we continue to receive from the National Institutes of Health (NIH), BlueWillow is now rapidly approaching Phase 1 human clinical studies in several programs."

The name BlueWillow Biologics is a nod to the company's roots as well as a commitment to the company's future as a developer of the next generation of vaccines. "Blue" is a subtle reference to the University of Michigan, where the company's nanotechnology was discovered. While "Willow" refers to willow trees, which are known to have deep, strong roots and large, protective branches.

"The NIH, Bill & Melinda Gates Foundation, State of Michigan, Michigan Nanotechnology Institute for Medicine and Biological Sciences, and the University of Michigan Technology Transfer Office have been instrumental in the advancement of BlueWillow's intranasal vaccine platform," added Mr. Peralta. "We are very grateful to each of these partners, as well as our core investors, for their support, guidance and investment in BlueWillow's promising future."

BlueWillow Biologics is a privately held biopharmaceutical company headquartered in Ann Arbor, MI, focused on developing and commercializing intranasal vaccines using its patented NanoVax technology platform. The technology employs a novel oil-in-water nanoemulsion adjuvant that is effective when administered via intranasal or intramuscular vaccination, and can elicit both mucosal and systemic immunity when applied intranasally.

SYGNIS Completes Acquisition of TGR Biosciences

SYGNIS AG recently announced the completion of the acquisition of TGR Biosciences (TGR), the Australian research reagents company. TGR and its highly complementary technologies and products along with its strong customer base will significantly contribute to the overall performance of the SYGNIS Group. SYGNIS is currently assessing the impact the acquisition will have on its previous 2018 full-year financial guidance and will announce this as soon as this review is complete.

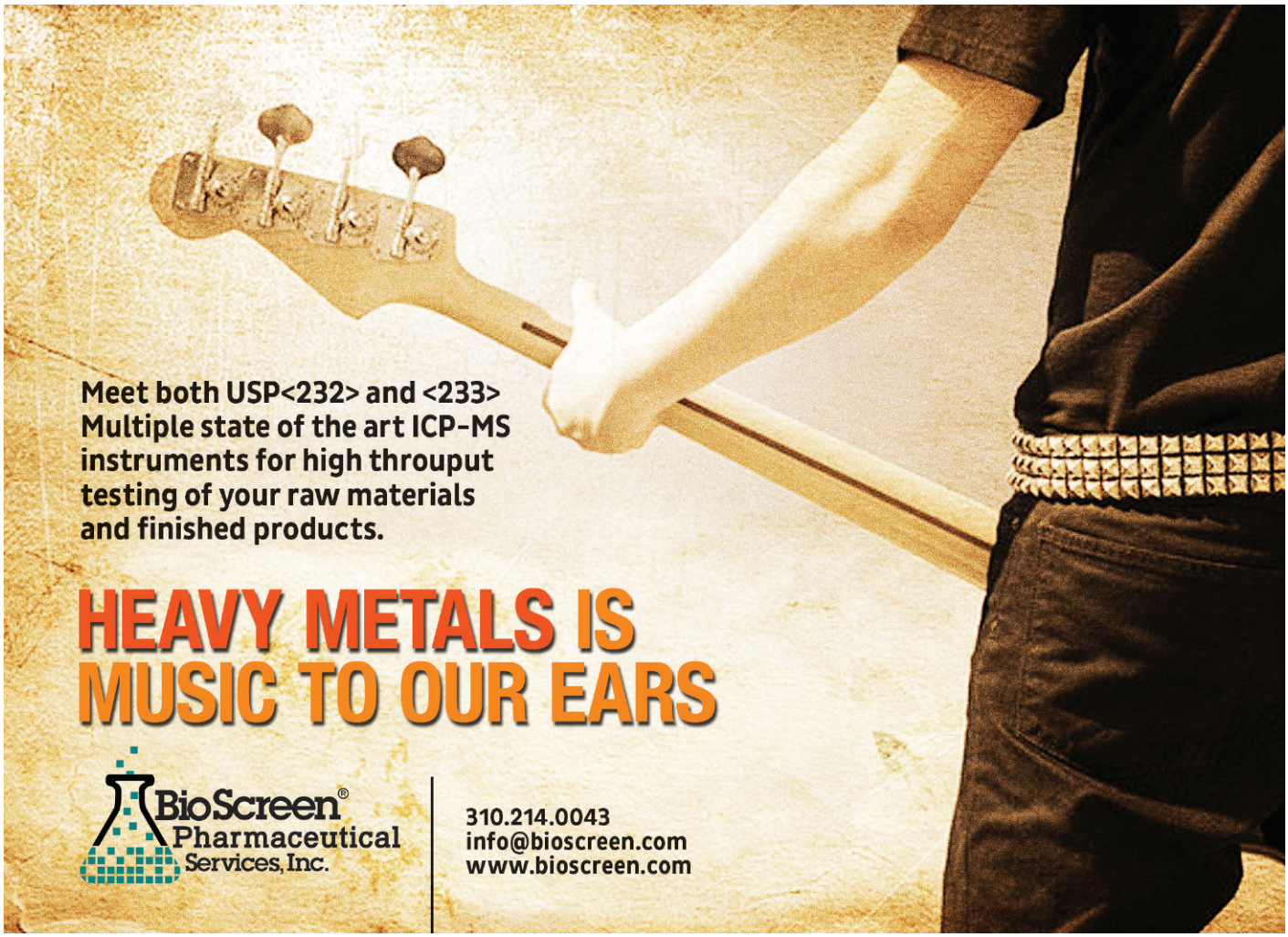
Dr. Heikki Lanckriet, CEO and CSO of SYGNIS, said "The acquisition of TGR Biosciences with its complementary business portfolio is a perfect fit for SYGNIS and an important step in our "Grow, Buy and Build strategy" – we are very excited about our joint future. Both TGR Biosciences and the SYGNIS Group will benefit from increasing sales and cross selling synergies, which will further strengthen our market position and provide further opportunities for growth."

The acquisition, priced in Australian Dollars at approximately EUR 10.1 million (net of cash acquired with the business) comprising cash, loan notes, and a share based earn out, brings TGR into the SYGNIS Group. The acquisition was financed by the recent capital increase, where SYGNIS raised gross proceeds of EUR 4.2 million in a private placement with institutional investors. Additionally, SYGNIS obtained a debt finance in the amount of EUR 2 million to complete the acquisition. SYGNIS has the right to exchange the debt finance into a mandatory convertible bond with additional option rights for approximately 1.4 million shares. The volume of the convertible bond and the conversion price will depend upon market conditions at the time SYGNIS utilizes such right if SYGNIS decides so which is likely.

TGR offers a strong complementary product portfolio, including patented best-in-class protein capturing technology, fitting with SYGNIS' range of products and services to support the immunology, genomic, and proteomic markets. TGR's technology and R&D facilities will be fully integrated into the SYGNIS group, and trade under the Expedeon brand in the near future.

SYGNIS develops and commercializes value-added, easy-to-use, reliable products for genomics and proteomics research based on its proprietary technologies, offering a wide range of solutions that address key challenges in molecular biology. With applications spanning the entire molecular biology workflow, the Group's cutting-edge offerings include easy-to-use off-the-shelf products as well as custom services, supporting scientists from academia through to commercial manufacturing.

SYGNIS' products are sold through a direct sales force and several distribution partners in Europe, the US, and Asia. SYGNIS AG has offices in Germany, Spain, UK, US, and Singapore, which trade under the Expedeon brand. For more information, visit www.sygnis.com.



Proteon Therapeutics & Lonza Extend Manufacturing Agreement

Proteon Therapeutics, Inc. recently announced a long-term contract extension with Lonza Pharma & Biotech for the commercial supply of investigational vonapanitase's active pharmaceutical ingredient (API).

"Proteon and Lonza have had a strong relationship for nearly a decade, and this amendment extends that relationship," said Timothy Noyes, President and Chief Executive Officer of Proteon. "The amendment provides Proteon with access to a top-tier manufacturing site for the long-term commercial supply of investigational vonapanitase after potential FDA approval."

"Lonza's microbial expertise and versatile assets will enable us to anticipate and deliver API for Proteon at this critical phase in the lifecycle of their therapy," said Marc Funk, COO Lonza Pharma & Biotech.

Karen Fallen, VP, Head of Clinical Development and Manufacturing for Lonza, added "It's always motivating for our teams to support biotechs like Proteon from Phase I studies through to commercialization and to see the impact for patients."

Lonza has manufactured API for Proteon at its microbial manufacturing facility in Visp (CH) since 2009. Initially, a small-scale process was transferred into Lonza's development labs for process optimization and consistency studies. The process was then scaled up to 1,000-L scale cGMP manufacture to support Proteon's early clinical studies and potential commercial requirements.

As Proteon worked to complete enrollment in its ongoing Phase 3 clinical trial, PATENCY-2, Lonza supported Proteon with three process validation batches at 1,000L commercial scale, each of which met the intended release criteria. If PATENCY-2 is successful, Proteon expects to include results from these validation runs in a potential Biologics License Application (BLA) filing in the second half of 2019, which Lonza will support.

Vonapanitase is an investigational drug intended to improve hemodialysis vascular access outcomes. Vonapanitase is currently being studied in a Phase 3 clinical trial in patients with chronic kidney disease (CKD). It has received Breakthrough Therapy, Fast Track and Orphan Drug designations from the FDA, and Orphan Medicinal Product designation from the European Commission, for hemodialysis vascular access indications. Proteon is also currently conducting a Phase 1 clinical trial of vonapanitase in patients with peripheral artery disease (PAD).

Proteon Therapeutics is committed to improving the health of patients with kidney and vascular diseases through the development of novel, first-in-class therapeutics. Proteon's lead product candidate, vonapanitase, is an investigational drug intended to improve hemodialysis vascular access outcomes. Proteon is evaluating vonapanitase in patients with CKD undergoing surgical creation of a radiocephalic arteriovenous fistula. Proteon is also evaluating vonapanitase in a Phase 1 clinical trial in patients with PAD.

Recent developments in next-generation biotherapeutics including antibody mimetics and novel scaffolds have spurred a renewed interest in microbial protein expression and manufacture technologies. Lonza's proven XS® Microbial Expression Platform combined with more than 30 years of process development and cGMP manufacture expertise make us an ideal partner to successfully support clinical and commercial programs.

2017

Global Drug Delivery & Formulation REPORT

The Drug Delivery & Formulation Pipeline

Part 4 of a 4-Part Series

Part 1: A Global Review

Part 2: Notable Product Approvals of 2017

Part 3: Notable Transactions and Technologies of 2017

Part 4: The Drug Delivery and Formulation Pipeline

By: Kurt Sedo, VP of Operations, and Tugrul Kararli, PhD, President & Founder, PharmaCircle

Introduction

The current pipeline can tell you everything you need to know about product approvals for the better part of the next decade. If it isn't in the pipeline at this point, it won't be approved before 2025 given the time required for clinical development and regulatory approval. Unfortunately, the pipeline is subject to all sorts of internal and external forces that create uncertain outcomes. Like a lottery, we may know all of the numbers, but we don't know which are the winners. Confidence in pipeline details drops as we look further back in the development pipeline, especially Phase 2 and earlier. Not only is there limited information available for these early stage products, in many cases, these products are not even fully "baked," with surprises yet to be discovered.

This pipeline review, centered on drug delivery and formulation products, looks forward and back 5 years, a total of 10 years. Looking back at product approvals is easy enough; approvals are publicly available along with considerable detail. The 5-year forward snapshot is captured by examining the products now in Phase 3 and Registration stages of development. The earliest of these pipeline products may be approved in a year or less, while others may still be 5 years from approval.

It's these Phase 3 and Registration products that will define the near-term direction of the pharmaceutical industry.

The analysis that follows is based on the PharmaCircle Pipeline & Products Intelligence module covering major market approvals and publicly disclosed development products. APPROVED for the balance of this article refers to products that received a first major market approval between 2013 and the end of February 2018. Numerically, this group excludes supplementary approvals for new indications or new dosage strengths. It does include new dosage form approvals of previously approved products, for example, a sustained-release formulation of a product that was previously approved as an immediate-release product. PIPELINE refers to products that were listed as either filed for Registration, or in active Phase 3 development as of the end of February 2018. Generics and biosimilar products are not included in either group.

Full Pharmaceutical Pipeline – the Big Picture

Figure 1 below provides a snapshot of APPROVED and PIPELINE products. A total of 1038 Approvals and 1661 Phase 3/Registration products are included in the analysis. The charts present results as percentages to improve clarity. Numbers can be estimated by multiplying together the percentages and total numbers.

With respect to the near-term future in terms of Indication, the emphasis clearly is on Cancer, at the expense perhaps of Infections and Endocrine/Metabolism.

Figure 1. APPROVAL and PIPELINE Products – Indications (Top 12)

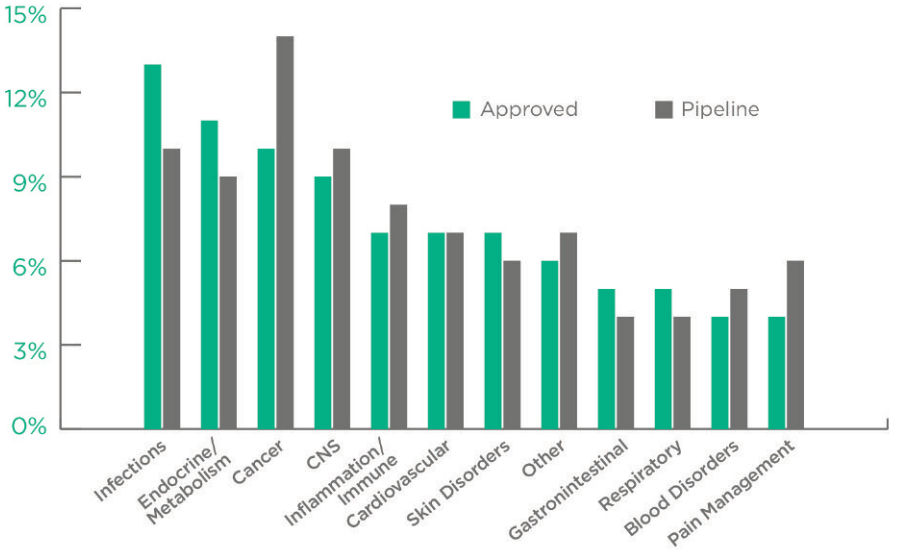
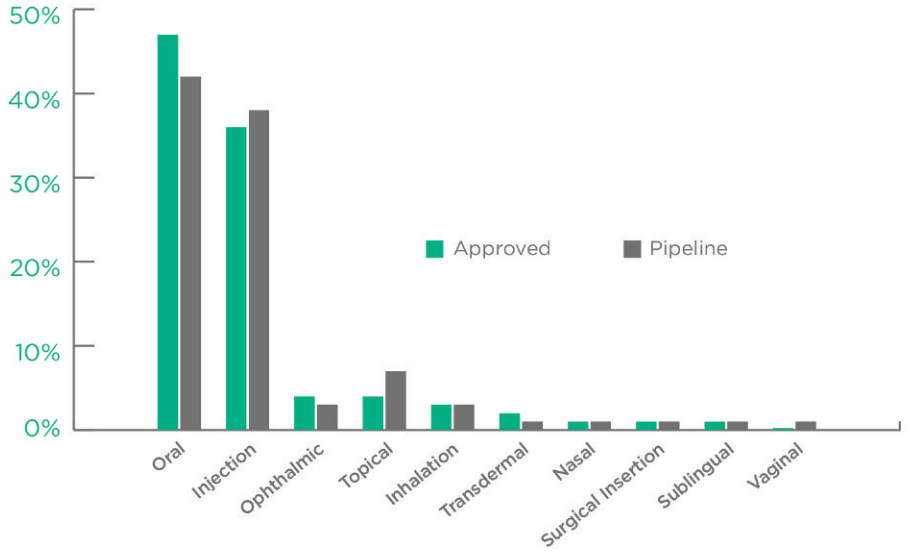


Figure 2 summarizes products as a function of Administration Route. There are no real surprises. There seems to be a drop in the development of PIPELINE Oral Products and an uptick in Injection Products, possibly reflecting the increasing interest and investment in Cancer Products.

Figure 2. APPROVAL and PIPELINE Products - Administration Route (Top 10)



There is an apparent shift in terms of Molecule Types being developed. PIPELINE products show a drop in Small Molecules with an increase in Antibody and Peptide products relative to APPROVED products. Cell and Gene Therapy Products represent a relative drop in the bucket yet are showing a strong increase in late-stage development.

Table 1. Products by Molecule Type

	small molecule	protein	antibody	peptide	polymeric	cell therapy	oligonucleotide	carbohydrate	gene
APPROVED	77%	8%	6%	4%	2%	1%	1%	0%	0%
PIPELINE	71%	7%	8%	6%	1%	3%	1%	1%	1%

One last macro trend may be revealed by a look at Combination Products. PIPELINE products seem to be headed toward fewer combination-type products. (Note: percentages are rounded to the nearest integer.)

Table 2. Product by Number of Molecules

	One	Two	Three	Four
APPROVED	84%	12%	3%	1%
PIPELINE	89%	9%	2%	0%

Drug Delivery and Formulation products accounted for a little less than 50% of APPROVED and PIPELINE products, 43% and 42%, respectively. (Drug Delivery and Formulation Products refer to products that incorporate one or more technologies to modify or improve the performance of a product. A simple injectable formulation and a simple compressed tablet would not be considered a Drug Delivery and Formulation Product.)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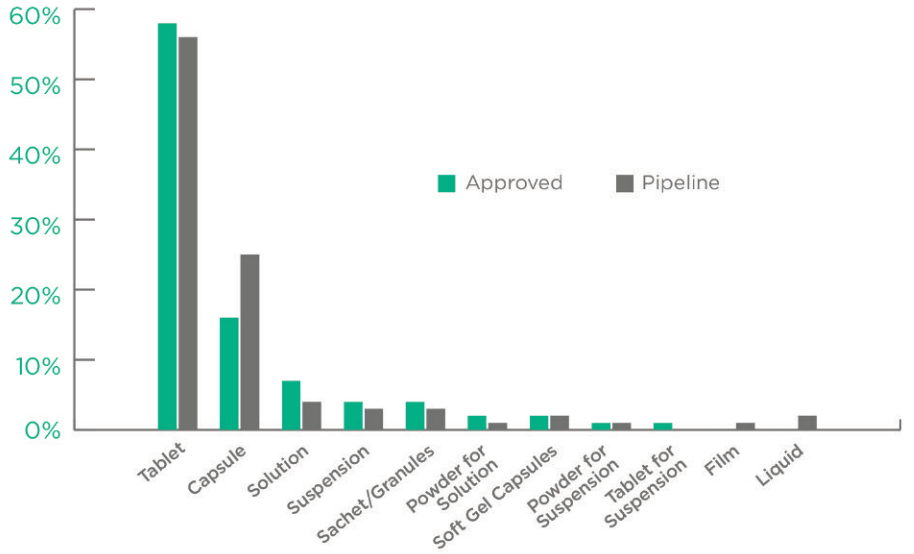
Oral Products

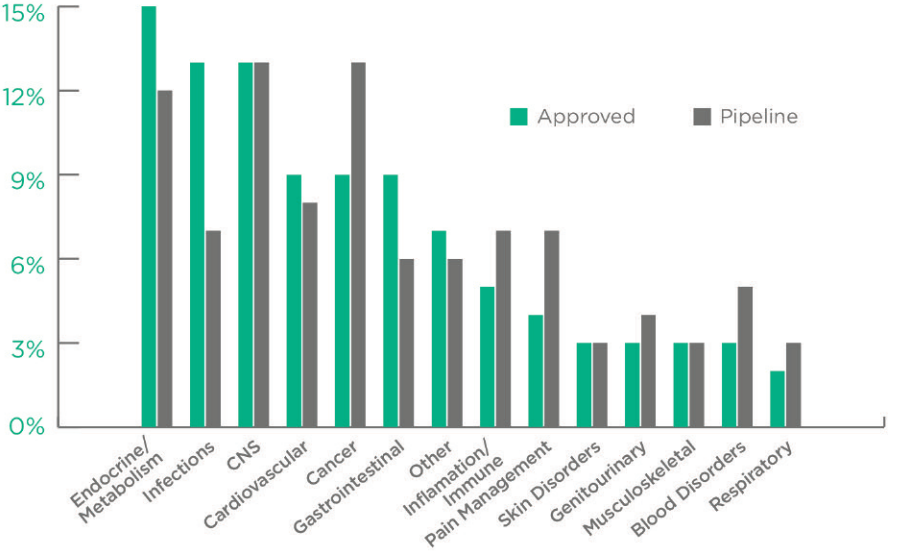
Oral Dosage forms comprise a wide range of dosage forms from Tablets to Films to Syrups. Tablets continue to be the number one dosage form, accounting for more than half of all recently approved and late-stage products but seem to be slipping as shown in Figure 3. The slippage in Oral Tablet products seems to be taken up by Oral Capsules.

Figure 3. Oral Dosage Forms (Top 11)



The indications addressed by Oral Products showed some interesting differences in terms of APPROVED and PIPELINE products with Infections showing the largest drop and Cancer the largest increase.

Figure 4. Oral Indications (Top 14)

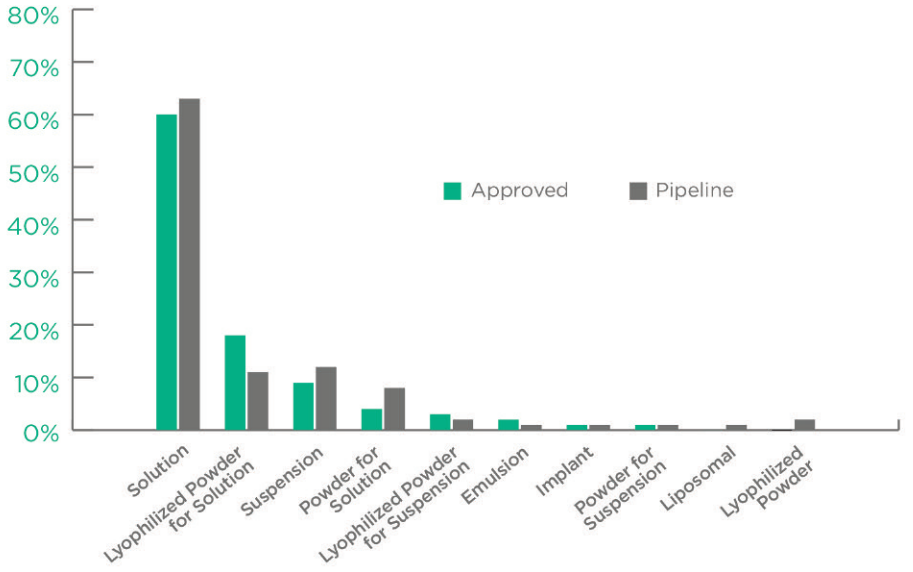


There was little difference in terms of the number of Oral Products that were labeled as drug delivery (27%) versus those that used no drug delivery or formulation technology (73%) in the two groups. The same situation was seen with Molecule Type for Oral Products, with Small Molecules accounting for 97% of APPROVED and 95% of PIPELINE products. There are fewer PIPELINE (17%) than APPROVED (25%) Combination Products.

Injectable Products

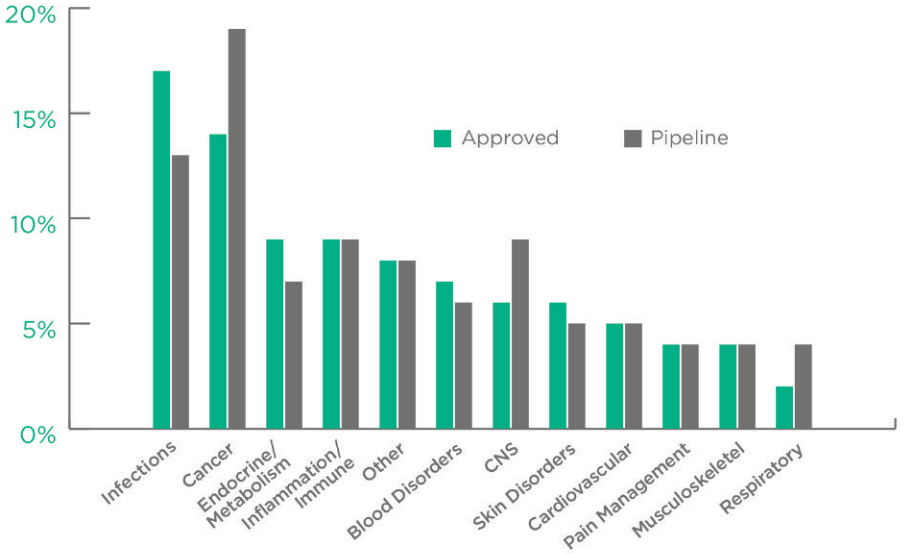
Injectable products cover a wide range of presentations from simple Injection Solutions to Lyophilized Powders to Implants. Injection Solutions, typically not involving a drug delivery and formulation technology, is the leading Dosage Form, accounting for more than 60% of all products, with a slight increase seen in PIPELINE products.

Figure 5. Injectable Dosage Forms (Top 10)



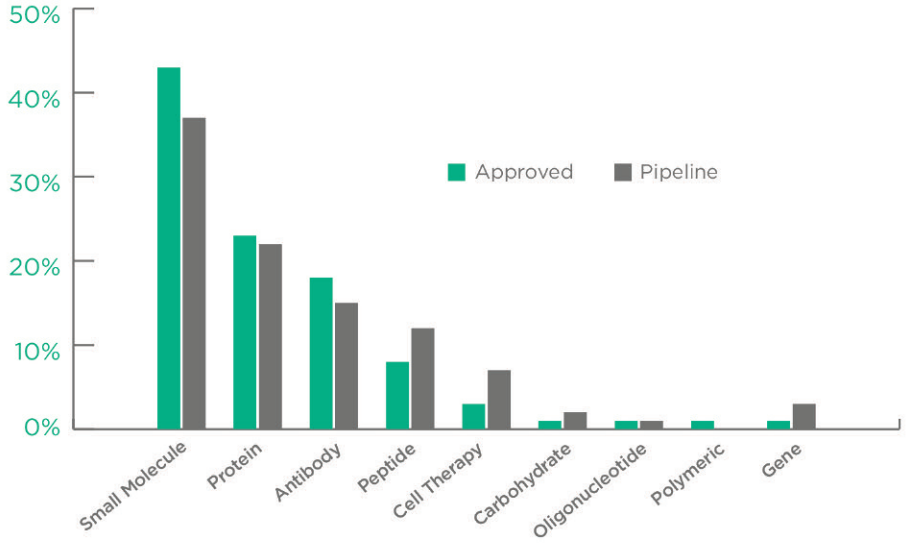
Indications addressed by Injectables show a shift in terms of emphasis when comparing APPROVALS and PIPELINE products. Cancer has become the number one indication for PIPELINE products, with a significant jump over Infections. Endocrine/Metabolism is trending down, while CNS is trending up.

Figure 6. Injectable Indications (Top 12)



A shift is also seen in Molecule Type with a drop in Small Molecule Injectable PIPELINE products. The difference is picked up by Peptide and Cell/Gene Therapy products, which together account for 20% of all PIPELINE Injectable products.

Figure 7. Injectable - Molecule Type



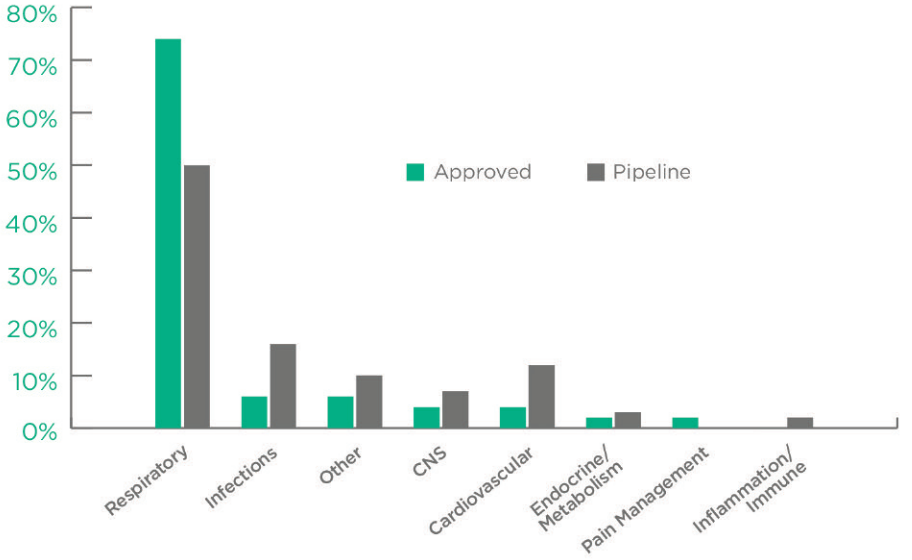
Drug delivery and formulation enhanced Injectables accounted for about 40% of all Injectable products, 44% of APPROVED and 37% of PIPELINE products.

Inhalation Products

Inhalation products represent a relatively small number of products, a bit fewer than 50 for each of APPROVED and PIPELINE products. An additional product or two in any category can significantly shift apparent trends.

Indications for Inhalation PIPELINE products show a shift relative to APPROVED products. The drop in PIPELINE Respiratory products (Asthma and COPD) is accounted for by an increase in products targeting Infections and Cardiovascular Disease, largely Cardiopulmonary Hypertension.

Figure 8. Inhalation – Indications (Top 8)



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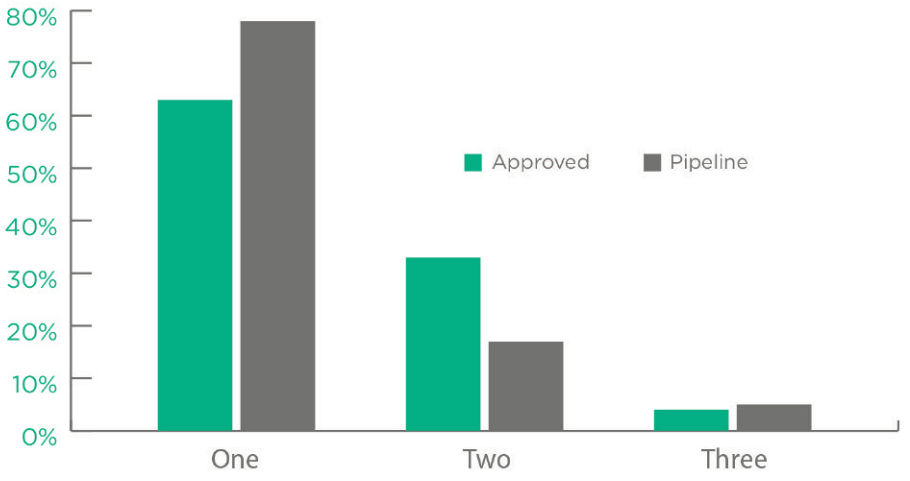
Molecule Type shows an increase in the number of Proteins, Carbohydrates, and Peptides in late-stage development versus what was approved in the past 5 years, with Small Molecules accounting for 98% of APPROVED and 80% of PIPELINE products. These larger molecule therapeutics are for the most part treating local and loco-regional rather than systemic conditions.

Combination Products are losing a little bit of their shine in terms of Inhalation PIPELINE products, perhaps as a result of the upswing in single-agent products being developed for Infection and Cardiovascular indications.

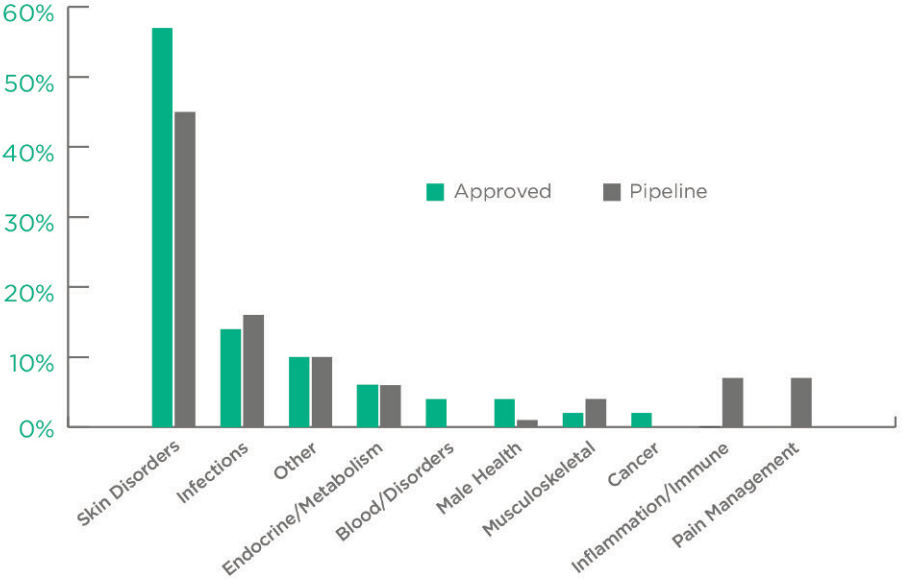
Figure 9. Inhalation - Number of Molecules



Topical Products

Topical products are a hodgepodge of products addressing local and systemic indications as reflected in Figure 10. A total of 40 APPROVED and 105 PIPELINE products were included in the analysis. There seems to be some trend toward products that address systemic type indications, Inflammation/Immune and Pain Management, at the expenses of more traditional Skin Disorder indications, such as Dermatitis and Acne.

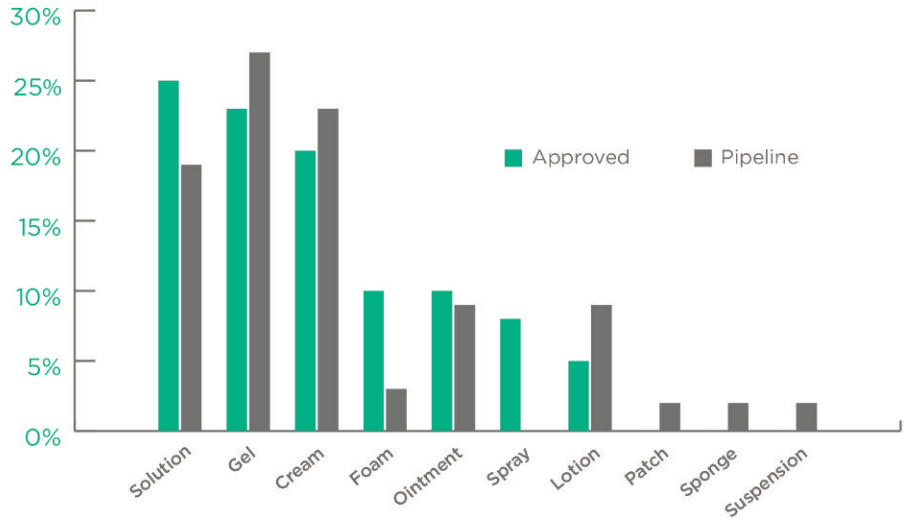
Figure 10. Topical Indications (Top 10)



Unsurprisingly, Small Molecules dominate the Topical product area representing a little less than 90% of all products for both APPROVED and PIPELINE products. PIPELINE products show a little more variety with Peptide, Oligonucleotide, and even Cell Therapy products in late-stage development.

With Topical products largely targeted to local or loco-regional indications, Dosage Forms are required to optimize patient acceptance and stability. This is reflected in the distribution of product forms that range from solutions to gels to creams to sprays and dressings.

Figure 11. Topical Dosage Forms (Top 10)



Combination Products represent a relatively small proportion of Topical products, 20% of APPROVED and 10% of PIPELINE products.

Concluding Thoughts

As noted in Part 2: Notable Product Approvals of 2017 of this 2017 Drug Delivery and Formulation Review, pharmaceutical products can be viewed as trees in the forest of a pharmaceutical ecosystem. Individual products in this ecosystem define the character and nature of the forest. Like any healthy ecosystem, things change naturally as products age and are replaced by newer, often different, varieties of pharmaceutical products. Looking at the forest of the pharmaceutical pipeline 5 years out, one finds that while it looks much like the forest of 5 years ago, there are hints of new species in the pipeline.

Indication focus is certainly evolving. A greater understanding of cancer, increasingly common successes, and the pricing premium afforded these products, has supported a shift in investment that is evidenced in the near-term pipeline. Drug delivery and formulation seems to be receiving less attention than it did 1, 2, and 3 decades ago. Many of the easy and most obvious new drug delivery and formulation opportunities, sustained-release oral and systemic transdermal products, have been realized. The larger challenges, delivering proteins and antibodies systemically through non-injection routes, have not yet been adequately addressed. This has forced the industry to incrementally improve the outpatient injection experience through better designed devices and extended dosing intervals. These

approaches are threatened by the development of novel small molecule products, such as the newer treatments for Hepatitis C, that forgo the need for large proteins and their delivery challenges.

Companies that can deliver next-generation drug delivery and formulation technologies will require considerable investment. It's not clear that there is an appetite for this type of investment in the absence of some substantial proof-of-concept. Examining 2017 early stage company investments related to drug delivery and formulation reveals that less than 10% of the funds, about $30 million, were targeted to what might be considered drug delivery technology; the balance being earmarked for product and corporate expenses.

A deeper pipeline of drug delivery and formulation with expanded features and capabilities will require breakthrough technologies. Breakthrough technologies require the necessary investment of time, effort, and money. Based on current evidence, it seems that it will be a decade before this next generation of drug delivery and formulation products are ready for approval, assuming of course the necessary investments are made sooner rather than later.

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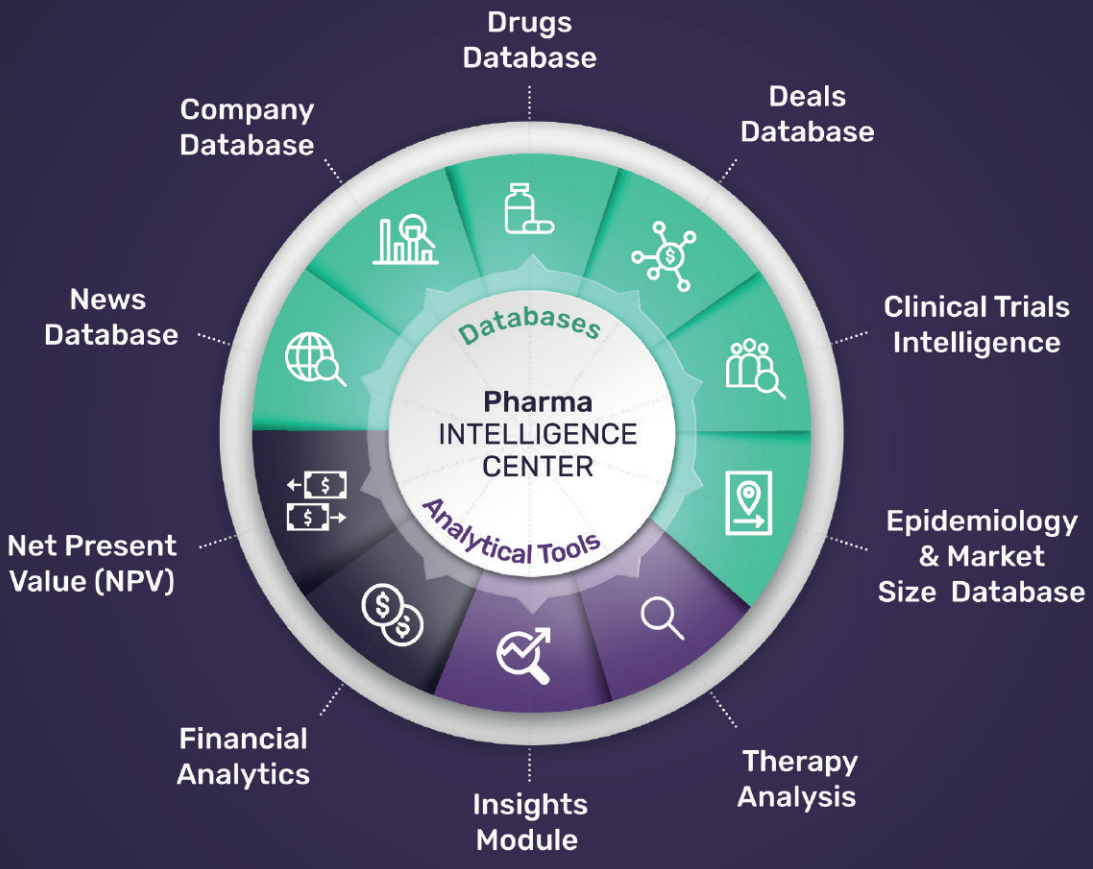

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ANTIBODY DISCOVERY

Why Understanding Immune Dysregulation is the Key to Drug Development

By: David S. Johnson, PhD

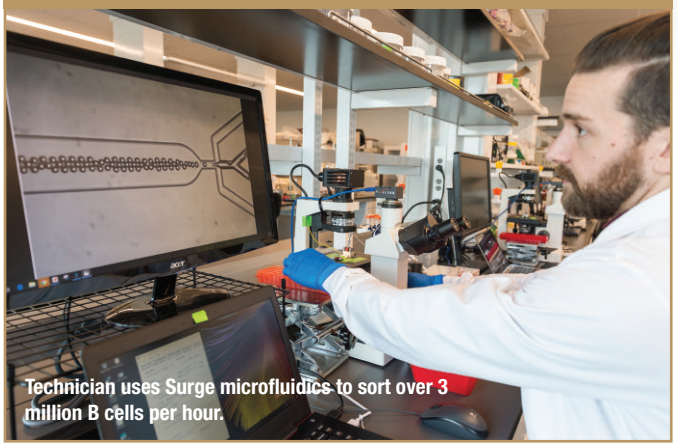
ABSTRACT

Antibodies have been used since the late 1980s as therapies to treat serious diseases, and demand is soaring to new heights today. However, conventional antibody drug discovery technologies are labor-intensive and slow. Pharmaceutical companies select drug candidates from just a small fraction of the antibodies that exist in a natural immune repertoire and have limited information on which candidates are the most promising. Additionally, identification and selection of drug targets remain an arduous process because conventional approaches to studying the immune system are not comprehensive. GigaGen Inc., based in South San Francisco, CA, has developed a unique insight into immune dysregulation through a proprietary technology known as Surge – a platform that quickly characterizes every cell in complex immune systems so that natural immune repertoires can be translated into medical treatments. The technology powers selection of drug targets, identification of drug candidates, and preclinical assessment of efficacy. GigaGen is using their insight into how the immune system functions to discover and develop drugs that solve disorders of immune dysregulation, including cancer and immune deficiency..

INTRODUCTION

Cancer. Rheumatoid arthritis. Primary immune deficiency. These and many more of the world's most devastating and widespread diseases involve dysregulation of the immune system. The body's network of cells, tissues, and organs that are designed to keep us healthy either fails to properly react against a dangerous "invader," or it over-reacts. In either case, the result is disease — and it can be deadly.

FIGURE 1



Technician uses Surge microfluidics to sort over 3 million B cells per hour.

Fortunately, throughout the past 3 decades, modern medicine has made great strides in treating dozens of immune-based conditions using antibody therapeutics. In the past 2 years alone, more than 20 of these drugs have gained FDA approval. Market research firms have estimated the global market for monoclonal antibodies at $85.4 billion in 2015, and expect it will soar to a value of $138.6 billion by 2024.

Since the human genome was sequenced, the number of well-characterized antibody targets has exploded. In particular, the field of cancer immunology has expanded rapidly. Antibodies targeting PD-1 and CTLA4 are among the most successful new cancer drugs in decades. These "checkpoint inhibitor" drugs specifically activate the immune system to target and kill tumor cells. At GigaGen and elsewhere, new insights into the tumor microenvironment continue to drive discovery of new checkpoint in-

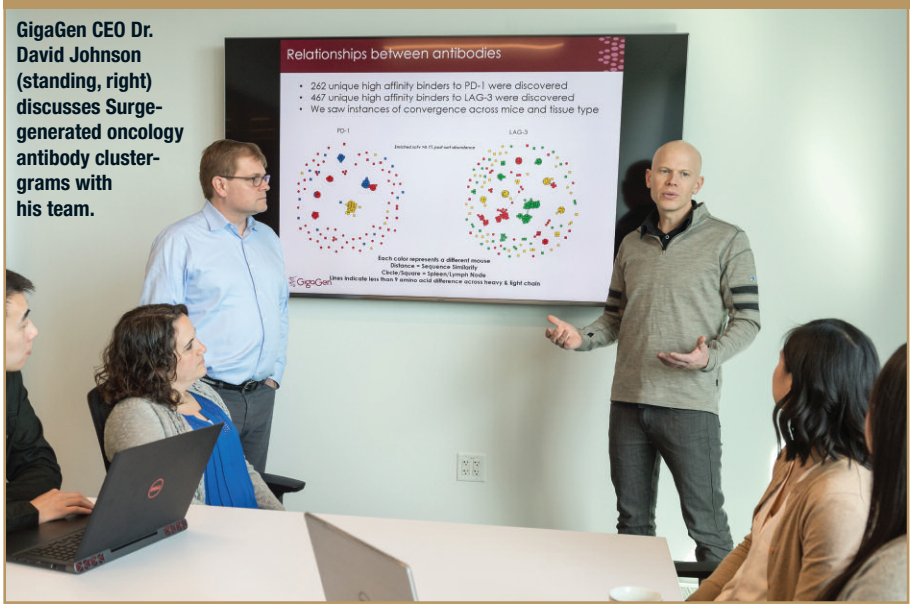
hibitor targets. There is tremendous competition to quickly turn these novel insights into drug pipelines.

However, immune systems are incredibly complex and still poorly understood. Immune cells respond to hundreds of stimulatory and inhibitory proteins, and constantly change during sickness and health. To understand immune systems, drug companies and academic researchers perform millions of cellular bioassays every day. Conventionally, studies of cell-cell interactions are performed in tissue culture plates, often on large, bulk populations of hundreds of thousands of cells rather than pairs of single cells. To scale these kinds of assays, drug companies and academics typically either severely reduce the ambition of their projects or spend millions of dollars on robotic automation. Eliminating this bottleneck could help unravel complex biological pathways, identify new targets, and eventually bring new innovative drugs to market.

Furthermore, once drug targets are identified, it's simply not good enough to have a single antibody against a single target in hand, which becomes the case when in-licensing from academia, for example. This is due to antibodies varying enormously in quality. In the checkpoint inhibitor field, for instance, a higher-affinity antibody is not necessarily a better drug choice. To block or activate immune receptors, antibodies must bind to the correct part of the target, and often the correct part of the target is not known upfront. Additionally, to avoid toxic side effects, antibodies must not bind non-specifically. On the other end of the spectrum, if an antibody binds too strongly to the correct target, there are also significant toxic side effects.

To build robust drug pipelines, most antibody drug discovery methods leverage mouse hybridomas. In this process, mice are immunized with a checkpoint inhibitor target and hybridomas are created from mouse B cells. However, this process is so inefficient that less than 1% of the original B cell diversity is retained. To compensate, large pharmaceutical companies have built massive, expensive robotic facilities. Still, discovery using this method requires years of effort. Small companies, on the contrary, lack hundreds of millions of dollars to build robotics and typically must choose a single target. They then will spend tens of millions of dollars to build a portfolio they hope will become competitive with large pharmaceutical companies.

FIGURE 2



GigaGen CEO Dr. David Johnson (standing, right) discusses Surge-generated oncology antibody clustergrams with his team.

WHEN CURRENT TECHNOLOGY IS LACKING, INNOVATE

Innovation is an alternative to spending large amounts of time and money on capital equipment. At GigaGen, we built an ultra-fast, ultra-efficient technology that characterizes every cell in complex immune systems, accelerating the selection of drug targets, identification of drug candidates, and preclinical assessment of drug efficacy. We call this technology Surge, and it leverages modern advances in microfluidics and genomics (Figure 1).

For target discovery, Surge is a method for massively parallel bioassays in picoliter droplets. We are able to study millions of cellular interactions, revealing changes in proteins that regulate the immune system. This facilitates discovery of novel pathways for modulating immune dysregulation, including genes that are involved in dysregulation of T and B cells. These genes may one day become novel drug targets. Previously, researchers might have incubated immune cells and their targets in 96-well plates, and then assayed cellular responses through methods such as flow cytometry, ELISA, or ELISpot. Such technologies are poorly suited for combinatorial analysis, for example, screening a millions-diverse panel of antibody-secreting cells against a millions-diverse panel of target cells. Thus, researchers using conventional technologies are forced to study only a few antibodies and targets at a time, severely constraining forward progress.

For antibody drug discovery, we immunize mice with an antibody target of in-

FIGURE 3

Technician prepares lymphocyte samples for Surge analysis.

terest. Then, we run the mouse B cells through our microfluidic platform to capture antibody sequences on a single cell level, but millions at a time. This process turns the efficiency of hybridomas upside-down, achieving more than 99% efficiency rather than less than 1% efficiency. We therefore mine for, and find, antibodies that no other technology is able to (Figure 2). Many of these antibodies could end up being the most efficacious or safest antibodies. The Surge technology is also proving to be much faster than conventional hybridoma technologies. Hybridoma screening involves several steps of assaying hybridoma pools, followed by single-cell cloning and expansion, finally followed by sequencing – a process that takes many months, or even years. The process we utilize with Surge determines the sequences of high affinity antibodies within days, allowing us to spend more time and financial resources on biological characterization and antibody optimization.

Though Surge works quickly, it took years to develop. GigaGen was founded in 2011 by myself and a Stanford colleague and immunology professor, Dr. Everett Hurteau Meyer. We have been supported by more than $10 million in NIH grant funding from the National Cancer Institute and the National Science Foundation and have generated numerous patent filings related to single cell droplet immune genomics, with the first issued patents in Europe and the United States in 2016.

In 2017, we published our work on mouse repertoires in the journal mAbs. We immunized wild type mice with the checkpoint target PD-1 and ran millions of B cells through our microfluidic system. We discovered hundreds of high-affinity PD-1 binders in only five mice in less than a month and utilizing only a single technician. These antibodies were often very rare, present at less than 0.01% of the original B cell repertoire. Even with the benefit of automated robot screening, hybridoma methods would have likely missed many of these rare antibodies. We examined 17 of the most promising antibodies in more detail and found nine antibodies that showed efficacy using our in vitro cellular assays. We are now performing affinity maturation in vitro on these antibodies for further non-clinical development.

The speed and convenience of our method results in a larger number of candidates for development pipelines. More mouse – or human – repertoires can be screened and this screening process can be conducted more exhaustively. This has substantial advantages for intellectual property because a program can choose a target and quickly identify hundreds of unique, validated binders. In theory, technologies such as Surge could also lead to shorter commercialization timelines.

We have also used our technology to discover rare, high-affinity binders in human repertoires, which was also highlighted in the journal mAbs in 2017. In this study, we used our microfluidic methods to create a large library of antibodies from the B cell repertoires of 52 healthy human donors. Yeast technology was then used to screen the library for binders against pneumococcus and influenza A antigens. Again, we found hundreds of high-affinity antibody binders – some as rare as 0.001% frequency in the original library. We followed up with efficacy assays using 19 of the antibodies. These antibodies had a surprising diversity of functionalities, reiterating the importance of capturing a wide variety of antibodies when developing a robust pipeline.

INSIGHT INTO IMMUNE SYSTEM FUNCTION LEADS TO NOVEL THERAPIES

Using Surge, we have been fortunate to come to understand disorders of immune dysregulation at a level that is unprecedented, spurring development of novel, revolutionary therapies for patients. We are first applying our insight to produce therapies targeting immune deficiency and cancer.

Immune deficiencies are characterized by the body's inability to properly make antibodies; consequently, patients with immune deficiencies are susceptible to recurrent and severe infections caused by viruses and bacteria that healthy individuals are able to fight off naturally. Patients with immune deficiencies are routinely treated with plasma-based drug products called intravenous immunoglobulin (IVIG), or high-titer variations referred to as "hyperimmunes," made by pooling Immunoglobulin G (IgG) antibodies from thousands of human donors. The plasma IgG drug industry is a $10-billion industry that has seen little innovation in decades, despite strong demand from doctors who treat immune deficiencies and their patients. Conventional plasma IgG drug products suffer several shortcomings that include constrained supply, risk of contamination by blood-borne pathogens and limited potency.

In our work to treat immune deficiency, we identified vaccinated individuals that were good responders to infection against pneumococcus, haemophilus, and viral influenza through immune repertoire profiling. This finding suggested development feasibility of therapeutics enriched against specific pathogens for patients with immune deficiency. Some of the data were published, and the work led to more than $6 million in funding from NIAID, and a $50-million investment and co-development deal with pharmaceutical company Grifols to develop recombinant polyclonal antibody therapies (Figure 3).

The ability to profile complex immune systems enabled us to develop and complete preclinical validation for the world's first recombinant polyclonal IgG product, a product that is advantaged over its plasma counterparts in that the risk for contamination from blood bourne pathogens is exceedingly low. Additionally, both production and batch-to-batch consistency can be controlled through manufacturing, which significantly reduces the risk of limited potency or supply shortage. Similarly, the recombinant nature of the drug enables us to engineer higher potency products than plasma-derived equivalents.

We have also applied our understanding of immune dysregulation to the field of oncology, selecting 17 checkpoint inhibitor targets to create antibodies against. Surge enabled us to immunize chimeric mice that produce fully human antibodies and run hundreds of millions of B cells from these mice through our microfluidic system. In a few months, we have discovered thousands of high-affinity binders to these 17 targets. We have synthesized and purified hundreds of candidates and have shown efficacy using cellular assays. These clinical candidates are all antibodies of natural-repertoire origin, with natural light- and heavy-chain pairing — factors that may increase drug developability and performance.

Our Surge technology and insight into cancer immunology has enabled us to build a highly competitive oncology drug pipeline from nothing, in a matter of months. The diversity of our portfolio gives us the unique ability to test combinations of repressor and activator agonists in vitro and in vivo before going to the clinic. This is critical because we have found through our research that immune repressive pathways can be repetitive, and it is therefore necessary to address multiple targets to avoid tumor escape from immunotherapy.

SUMMARY

At GigaGen, we envision a future in which the only hurdle in drug development is the clinical trial. Our technology has enabled us to build a robust portfolio of checkpoint inhibitor antibodies in a matter of months, and lay the groundwork for recombinant polyclonal IgG drugs poised to revolutionize treatment of immune deficiencies. For the first time ever, it's possible to understand immune response to disease with incredible breadth and detail and use this power to create life-saving therapies.◆

BIOGRAPHY

Dr. David S. Johnson is CEO and Co-founder of GigaGen Inc. He is an inventor, entrepreneur, and expert in single-cell immunology with a track record of bringing new medical technologies to market. At GigaGen, Dr. Johnson has served as Principal Investigator for 16 grants from NSF, NCI, and NIAID, including seven Phase II projects. These grants led to about $52 million in partnerships with several established pharmaceutical companies, including Grifols, Novartis, and Merck. Prior to GigaGen, Dr. Johnson was among the founding members and COO of Natera, a reproductive molecular diagnostics firm that went public in 2015 (NASDAQ: NTRA). At Natera, Dr. Johnson was responsible for all clinical operations, laboratory research, clinical studies, and clinical product development. Prior to Natera, he was the ENCODE Project Director at the Stanford Human Genome Center. Dr. Johnson earned his BS in Biology from Duke University, his PhD in Genetics from Stanford University, and his MBA from the Haas School of Business at the University of California, Berkeley. Dr. Johnson's work has been published in many journals, such as *Science, Nature Methods, Blood,* and *mAbs.*

PEPTIDE DELIVERY

The Endometriosis Enigma – Why Can't There Be a Pill for That?

By: Joel Tune, MBA

INTRODUCTION

Affecting approximately 6 million women in the US, endometriosis is one of the most common gynecological disorders and occurs when the endometrial lining tissue begins to grow outside the uterus, leading to lesions. These lesions may grow on the ovaries, fallopian tubes, and other areas of the uterus, causing severe pain.

Leuprolide, marketed under the brand name LUPRON DEPOT® (leuprolide acetate for depot suspension), has demonstrated in the clinic and practice to be an efficacious treatment for endometriosis. However, the current parenteral route of administration limits the drug's utilization due to the irreversibility of the depot injection, which stays in the body for 30 to 90 days, and the pain and inconvenience of the injections. A daily oral leuprolide tablet could offer a more patient-friendly alternative to monthly depot injections, potentially encouraging physicians and patients to utilize the medication earlier and more often. Market estimates suggest such a drug could produce revenues in excess of $600 million annually in the US.

So why isn't there a pill for that? The challenge of capturing the potential of orally delivered peptide therapeutics is ongoing as researchers look to develop formulations that can overcome both business and technical challenges.

The business challenge is pretty straight forward; select peptides and clinical indications that are appropriate for oral delivery. Practical considerations, such as whether the orally delivered peptide will enhance patient compliance, increase treatment options, and boost marketability, should have priority because without clear medical and business advantages, there is little motivation to make the investment in time and resources to transition from an injectable. Market and patient research indicates that an oral formulation of leuprolide for endometriosis would meet these criteria.

The technical and clinical challenges are significant. There are numerous technologies currently in development that are designed to enable the oral delivery of peptides. Though each has its unique set of properties and capabilities, all must overcome key obstacles to successfully deliver peptides via the oral route.

First, the oral formulation must remain intact in the highly acidic environment of the stomach. Once through the stomach, the tablet design must then promote dissolution in the higher pH environment of the small intestine, while simultaneously protecting the peptide payload from degradation by protease enzymes. Finally, mechanisms must be present that facilitate the absorption of the peptide into the relatively impermeable intestinal epithelium.

However, even with all the boxes checked, oral delivery may not be an option unless one can achieve therapeutically relevant bioavailability.

Peptides and proteins are high molecular weight biopolymers and contain both hydrophilic and hydrophobic appendages in their structure. These properties make it difficult for peptides to be absorbed by the intestine. In addition, the stomach and intestine are designed to digest peptides and proteins into usable components. Simply said, our bodies recognize peptides as food when ingested. Protecting the therapeutic peptide long enough to deliver it to the right place in the system and in the right conditions to maximize absorption are the keys to successful delivery of an oral peptide.

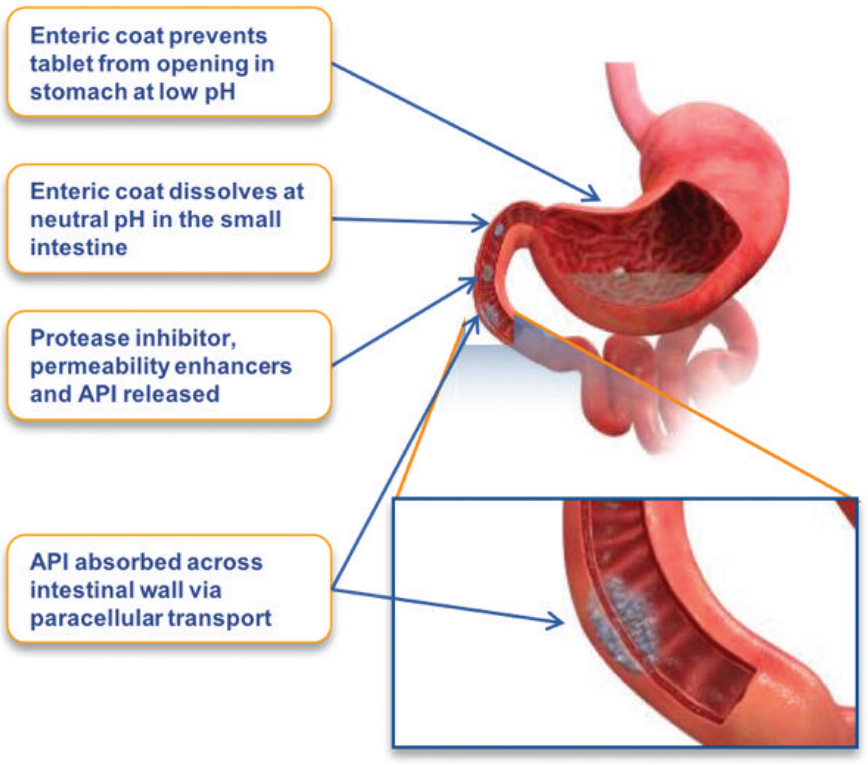
The question then is this: Is there a way to overcome the drug development challenges in engineering an oral formulation of leuprolide in a manner that allows one to effectively and efficiently capitalize on the market/patient potential of such a drug product?

HISTORY

We know that proteins and peptides are the building blocks of life and recently have been identified as a very promising basis for targeting a range of diseases. Throughout the past 3 decades, and especially the past 10 years, there has been a rapid growth in the development of therapeutic proteins, with a significant increase in the number of protein-based drugs on the market.

Peptides occupy a therapeutic niche between small molecules and large biologics, and are generally classified as being a chain of amino acids containing 40 amino acids or less. Currently, the disease areas driving the therapeutic use of peptide drugs are oncology (driven by a rising mortality and need for chemotherapy replacement) and metabolic diseases. The treatment of metabolic diseases via peptide therapeutics has largely centered around the epidemic growth in type 2 diabetes. Examples of such injectable peptide drugs on the market today include Byetta, Victoza, and Trulicity, which are part of the family of glucagon-like peptide-1 (GLP-1) receptor activators. These peptide drugs work by interacting with a receptor on the surface of pancreatic beta cells to stimulate the release of insulin. In addition to metabolic disease and oncology, the movement of the pharmaceutical industry into rare diseases and orphan drugs has also been extended to peptides, and peptides are being further targeted at infectious diseases and inflammation. Historically, all of these peptide drugs have been administered by injection.

FIGURE 1



The mechanism for oral drug delivery presents certain challenges. While the GI tract degrades and digest peptides, there is poor permeability through the intestinal cell layer due to interaction with efflux transporters. As shown, enteric coating prevents the tablet from opening in the stomach, allowing it to be dissolved in the small intestine where the drug can then be absorbed across the intestinal wall.

Research has demonstrated that peptide therapeutics can offer several advantages that are distinct and desirable. Peptides serve a highly specific set of functions in the body that cannot be mimicked by simple chemical compounds. Thus, compared with small-molecule active pharmaceutical ingredients (APIs), peptides are able to exhibit increased potency and selectivity due to specific interactions with their targets. As a result, peptides have the potential for decreased off-target side effects and decreased systemic toxicity. Moreover, because the body naturally produces peptides, peptide-based therapeutics are often well-tolerated and are less likely to elicit immune responses.

Given their attractive pharmacological profile and intrinsic properties, peptides represent an excellent starting point for the design of novel therapeutics, and their specificity has been seen to translate into excellent safety, tolerability, and efficacy profiles in humans. Furthermore, peptide therapeutics are typically associated with lower production complexity compared with protein-based biopharmaceuticals.

Though peptide therapeutics offer numerous advantages, and the growth of such drugs is strong, there remains a significant gap between "market actual" and "market potential." This is largely attributable to challenges with the route and method of delivery of peptide drugs.

The interest in oral peptides is driven by three dynamics – patient compliance, prescriber preference, and market expansion. As one can appreciate, frequent injections and low patient acceptability make parenteral administration of peptide-based drugs less desirable. This is especially true in long-term treatment regimens. As a result, pharmaceutical developers continue to explore alternate routes of delivery for peptide therapeutics that have the potential to maintain the drug's potency, while enhancing the ease of administration, patient compliance, and market penetration.

Against this backdrop, the oral delivery of peptides, such as leuprolide, has caught the imagination of drug developers far and wide. Long hailed as the "Holy Grail" of drug delivery, orally administered peptides offer vast potential but also present considerable development challenges.

CHALLENGES & OPPORTUNITIES

In developing its oral leuprolide tablet, biotechnology company Enteris BioPharma utilized a technology platform designed to provide protection against the harshness of the digestive system and then promote absorption of the leuprolide into the bloodstream. First, to overcome the stomach's highly acidic environment, the oral tablet was encapsulated in an enteric coating. Simple in concept, an enteric coating is a polymer barrier applied to an oral medication that prevents its dissolution in the gastric environment.

Enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, yet dissolves at the higher pH of the small intestine and at locations within the intestinal tract to enable optimal drug absorption. A variety of materials can be utilized as an enteric coating, provided the material shields the peptide drug in the stomach and enables its release in the intestine where absorption into the bloodstream can occur.

Protecting against the acidic gastric environment and enabling dissolution in the small intestine is but the first hurdle that must be addressed. The next goal is limiting proteolytic degradation in the jejunum, which is a considerably more difficult (and critical) proposition. Given that many peptides are highly vulnerable in the soluble form to peptidases in the lumen prior to reaching the systemic circulation, the challenge is to prevent the breakdown of the peptide. Though it is difficult to completely inhibit the actions of luminal proteases, scientists at Enteris BioPharma utilized protease inhibitors to create a protective microenvironment for its oral leuprolide tablet. Without such protective measures, the protease enzymes would immediately act upon the leuprolide, breaking it down for ingestion into the bloodstream; no different than a protein consumed as food.

Shielding against the digestive system is paramount to administering a peptide orally, and success in developing an efficacious oral peptide (one that elicits the desired therapeutic response comparable to or exceeding the standard of care) ultimately hinges on whether the peptide is absorbed through the intestine and enters the bloodstream as an intact chemical species. As referenced previously, peptides have relatively large molecular weights and hydrophilicity, resulting in poor penetration across the intestinal epithelium. This may be the most challenging barrier to oral peptide delivery.

As peptides reach the intestinal epithelium, they first encounter an exogenous mucus gel layer containing proteases and antibodies, which together reduce the rate of diffusion to the epithelial surface. Attempts to overcome mucoadhesion have focused on incorporation of mucolytics or use of hydrophilic PEGylated nanoparticles, which avoid entrapment in mucus glycoprotein meshes. An alternative approach is to exploit mucoadhesion to increase the residence time of the dosage form in the small intestine.

However, greater success has been

TABLE 1

Advantages	Ovarest®	Lupron
Drug Delivery	Oral	Injectable
Side Effects	If side effects occur, therapy can be stopped quickly as it only takes days to leave the body.	If side effects occur, therapy can't be stopped quickly as it can take one to three months to leave the body depending on the injection
Pain	No pain or injection site reactions due to its oral formulation	Pain and injection site reactions
Logistics	Dispensed like a regular prescription	Involves multiple visits to the doctor in order to undergo therapy

Current Standard of Care of for endometriosis patients requires multiple visits to the doctor to undergo multiple injections. In addition, potential side effects can last a while as it takes months for the medication to leave the body long after the injections stop. Oral delivery of Ovarest means that pills can be dispensed like a regular prescription. If needed, therapy can be stopped quickly, and it only takes days for the medication to leave the body.

achieved via the use of permeability enhancers, such as lauroyl-l- carnitine chloride (LLC), palmitoyl carnitine chloride (PCC), and sodium taurodeoxycholate, which facilitate peptide entry into the bloodstream. Such permeability enhancers function by enabling the transport of peptide molecules through the epithelium via passive movement across the epithelial tight junctions.

Finally, after overcoming these obstacles, the successful developer of an oral peptide must accept that the bioavailability of an orally delivered peptide will be less than that of a comparable dose of a parenterally delivered peptide. Even the best oral peptide formulas are known to have relatively low bioavailabilities of ≤10%. As such, higher oral formulation doses are required to obtain the same therapeutic effect achieved with an injectable formulation.

For example, Enteris BioPharma recently announced interim results of a Phase 2a trial of its oral leuprolide tablet (Ovarest®) being developed to treat endometriosis (initial indication) comparing once- and twice-per-day doses of a 4- mg oral tablet with a single, monthly depot injection of LUPRON DEPOT 3.75 mg. The daily dose of the Enteris oral tablet is therefore higher than the monthly LUPRON DEPOT injection dose. Data from the study, utilizing Enteris' proprietary Peptelligence® platform, indicated that significant suppression of estradiol (E2), demonstrated a measurable pharmacodynamic effect that is tightly correlated with efficacy in endometriosis. A higher dose 10-mg tablet arm, administered twice-per-day of the Phase 2a study is currently underway, and Enteris expects to be in a position to announce the results from that arm in early July 2018.

The Peptelligence® platform is a novel formulation technology that enables oral delivery of molecules that are typically injected, including peptides and BCS class II, III and IV small molecules. The positive interim results from the Phase 2a clinical trial are a significant advancement towards Enteris' goal of developing the first-ever oral leuprolide tablet for the treatment of endometriosis (initial indication).

Though orally delivered peptides, such as Ovarest, have considerable value potential, developers must carefully consider the practicality of transitioning a peptide to an oral form based on the cost of goods. Simply put, the cost of the additional API (and production) must be less than the expected market expansion for an oral formulation. Considerable research by Enteris indicates that Ovarest meets this "Goldilocks sweet spot," but not all peptides do.

SUMMARY

Ultimately, not all peptide therapeutics are appropriate for oral administration due to various constraints, from physiochemical to economic. However, for those that meet the necessary criteria, advances in formulation technologies coupled with favorable market dynamics will continue to drive interest across the entire prescription drug spectrum for safe and effective orally administered peptide therapeutics. ◆

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

BIOGRAPHY

Joel Tune currently serves as Enteris BioPharma's Executive Chairman of the Board of Directors and Chief Executive Officer. He joined the company in July 2013, initially serving as the Executive Chairman of the Board of Directors. In January 2016, he assumed the role of CEO. He is a highly seasoned executive with an extensive knowledge of strategy, operations, and business development. Prior to joining Enteris BioPharma, he spent 28 years with Baxter HealthCare Corp. in roles of increasing responsibility within product development, sales and marketing, strategy, mergers and acquisitions, and general management. His last role at Baxter was as Vice President and General Manager of the BioPharma Solutions Business, with global responsibility for the rapidly growing $800M franchise. Since leaving Baxter, he has served as an independent consultant to a variety of private equity, venture capital, and healthcare start-up firms, including serving on the Board of Directors for Unigene Laboratories and Epic Therapeutics. Mr. Tune earned his MBA from Marquette University and his BS in Biomedical Engineering from the University of Louisville.

MICROFLUIDS

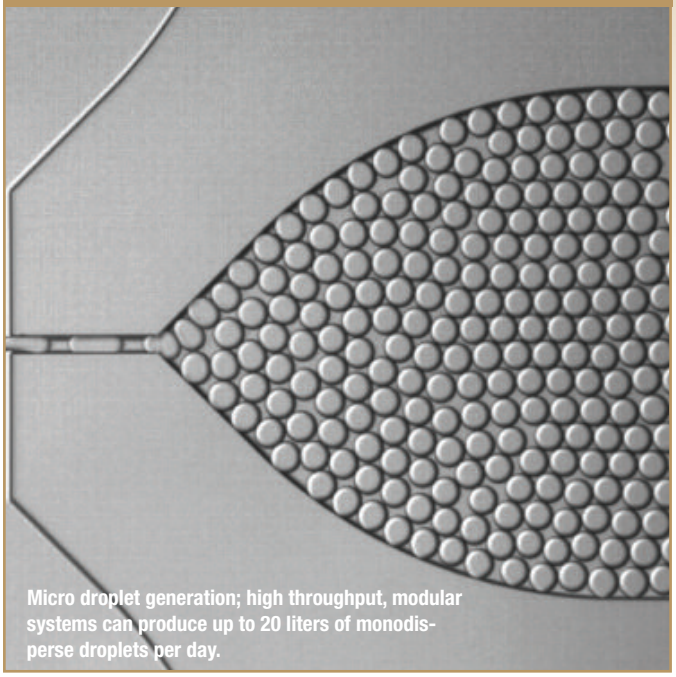
Taking a Microfluidics Approach to Drug Delivery

By: Richard Gray, MA, and Pavel Abdulkin, PhD

ABSTRACT

Polymer encapsulation has long been recognized as a way of improving the uptake and release of small molecule drugs, and has more recently been used to enhance the stability and bioavailability of biologics. Unfortunately, despite the benefits, traditional emulsion particle manufacturing techniques are laborious, inefficient, and inconsistent, limiting the widespread application of microparticle drug delivery vehicles. Recent advances in both manufacturing and polymer composition are addressing these issues, leading to a new wave of microencapsulated drugs. This article looks at how microfluidics is changing the drug development sector and explores an exciting new non-encapsulating microparticle-based approach that offers "tunable" release of the active pharmaceutical ingredient (API).

FIGURE 1



Micro droplet generation; high throughput, modular systems can produce up to 20 liters of monodisperse droplets per day.

INTRODUCTION

The concept of encapsulating a drug within a polymeric particle for delivery is not new, and it has been common practice for over 20 years to use micro- and nanoparticles as drug delivery vehicles. Drug encapsulation within polymer spheres offers a number of benefits over conventional dosage forms. First, it can protect the API from enzymatic or acidic degradation. It also leads to a more uniform absorption rate, as the particles are distributed over a greater area of the gastrointestinal tract. In addition, dividing a dose across multiple particles improves safety and reduces the risk of toxicity in the event of defective delivery. While controversial, there is also some disputed evidence to suggest that microparticles preferentially congregate in tumor tissues – the enhanced permeability and retention effect – offering the possibility of more targeted drug treatments. Microencapsulation also provides a solution to an ongoing problem that plagues pharma companies; many promising small molecule drug candidates are hydrophobic and poorly soluble in water, which makes them unusable. Encapsulation overcomes this barrier, helping a candidate drug's transition from discovery to development.

CHANGING TACTICS

Controlling microparticle size is important in drug microencapsulation, not least because particles that are too large can block an injection needle. The diameter of the polymeric particles also determines the drug-release profile and rate of polymer degradation; large droplets may release the drug too slowly, resulting in a non-therapeutic dose, while small beads may release the drug too quickly, causing a spike and potentially harmful side-effects. Effective dosing therefore requires the administration of monodisperse particles with a carefully chosen diameter contain-

ing the correct dosage of API. This is difficult to achieve in commercial-scale production, as particle size is subject to statistical control, and the resulting polydisperse particles require additional size selection steps to isolate appropriate microparticles, such as selective filtration.

Traditional batch approaches rely on using mechanical stirring or sonication to mix an aqueous phase containing the dissolved API and a surfactant with a polymer in an organic phase, creating an emulsion. Unfortunately, these batch processes suffer from low and uneven API encapsulation, broad particle polydispersity, and a lack of batch-to-batch consistency, leading to very low yields and productivity. Luckily, all of these issues can be ameliorated using a continuous flow microfluidics approach.

Microfluidics offers carefully controlled mixing of aqueous and organic phases to create homogeneous populations of monodisperse micro- or nanoparticles at flow rates of up to tens of milliliters per minute. The ability to "fine tune" the physical properties of the resulting particle population by adjusting the total flow rate, polymer concentration, aqueous-to-organic flow rate ratio (FRR), and use of a co-solvent is another major benefit of a microfluidics approach. This allows particle size to be tailored to individual applications – from 100 nanometers to 100 micrometers – without changing the hardware set-up. If fully optimized, it also offers virtually 100% encapsulation, compared to about 30% encapsulation efficiency for a typical batch technique, avoiding the waste of large quantities of expensive APIs.

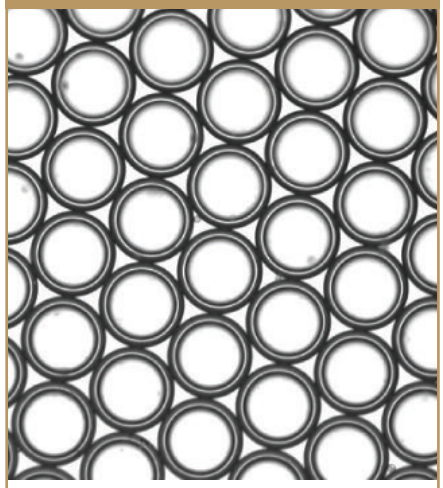
PLUG & PLAY SIMPLICITY

The increased uptake of microfluidics for drug delivery applications is largely a result of a rise in commercial availability of standardized hardware set-ups – connectors, chips, and pumps – from suppliers, such as Dolomite Microfluidics. These products have helped to move microfluidics from a niche method into routine laboratory use, enabling researchers to focus their time on applications rather than developing the technology. This technology has now become so ingrained in the industry that in 2015, the US FDA recommended the production of all microencapsulated drugs be migrated to continuous flow manufacturing techniques. The transition coincides with the commercial development of high throughput, modular systems that can produce up to 20 liters of monodisperse droplets per day – offering production speeds and scales comparable to batch techniques. The timely combination of the right technique, commercially available tools, and business interest has encouraged the rapid adoption of microfluidics for drug encapsulation.

THE NEXT CHAPTER

As it stands, an encapsulated drug is released from the particle matrix via diffusion or osmosis, or through decomposition or enzymatic digestion of the polymer. ProLynx, a biotech start-up in San Francisco, CA, is developing a new platform for drug delivery using cleavable linkers to control drug release and the subsequent degradation of the hydrogel microparticle. In contrast to encapsulation methods, the release rate of the covalently tethered drug is completely tunable and independent of polymer degradation. This technology has been shown to extend a drug's biological half-life ($t_{1/2}$), and the company has a growing intellectual property portfolio for the delivery of small molecule, peptide, and protein APIs.

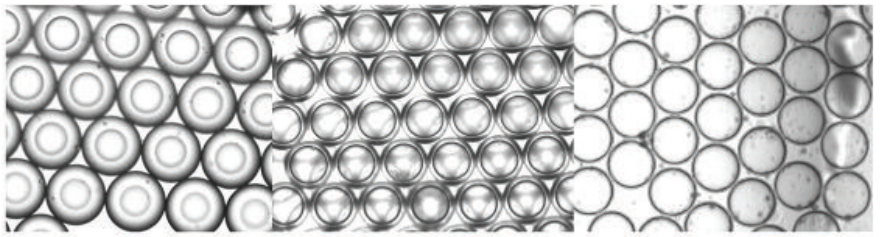
FIGURE 2



Double emulsion; Double emulsions can be used as a carrier of active ingredients for controlled drug delivery.

At the heart of the new technology is a cleavable linker tethering the drug to a tetra-PEG-hydrogel microparticle, comprising a carbamate group with an acidic carbon-hydrogen bond on the beta-carbon. The acidity of the C-H bond is determined by an electron withdrawing "modulator" group – such as a methylsulfonyl ($MeSO_2$) or nitrile (CN) – which controls the rate of a beta elimination reaction to free the unmodified drug from the microparticle. Analogous yet slower-cleaving carbamate linkers are incorporated into the PEG-hydrogel microbead crosslinks, enabling degradation of the bead to be coordinated to occur after the drug is released. Manipulating the modulator for both the drug tether and PEG-hydrogel crosslinking offers a wide $t_{1/2}$ range – from hours to years – for any given API.[1] This places the drug-release profile under tunable, chemical control, rather than being dependent on microparticle size and composition.

FIGURE 3



Double emulsions made using Dolomite products; a range of highly consistent double emulsions can be produced using commercially available systems.

A key part of the company's manufacturing process is the production of the PEG-hydrogel microparticles, which is carried out using a custom-made glass Telos® 2 Reagent Chip from Dolomite Microfluidics.[2] The chip's seven 50-micrometer channels enable ProLynx to produce microparticles with a 40-micrometer diameter at a rate of ~4,000 droplets/sec/channel, equivalent to 8 ml/hour. The Telos system allows up to 10 Telos modules to be assembled in parallel for easy scale-up, offering identical conditions for up to 70 droplet junctions.

To date, the company has published papers on its work with exenatide – a peptide for treating Type II diabetes – and octreotide, which is an FDA-approved peptidic somatostatin (SST) agonist used to treat acromegaly and neuroendocrine tumors.[3,4] In addition to working with smaller molecules, experiments with a single chain antibody fragment (25 kDa) have extended its $t_{1/2}$ to be comparable with monoclonal antibodies.[5]

SUMMARY

Drug delivery will continue to be a growing market and area of research, and there are still many challenges that present opportunities to develop innovative technology-based solutions. The excellent control of particle size and composition offered by microfluidics has established the technology as a reliable and reproducible resource for the generation of monodisperse, microencapsulated drugs. Combined with its scalability and the growing commercial availability of customizable hardware solutions, microfluidics will provide a platform for experimentation and discovery in the years to come. ◆

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BIOGRAPHIES

Richard Gray is Director at Blacktrace Group, the parent company of Dolomite Microfluidics, Particle Works and Syrris. He founded Syrris Ltd with Mark Gilligan in 2001, moving to the USA in 2004 to manage the group's US subsidiaries. His background includes fast-track product and process development in consumer, medical device, and industrial sectors. Before Syrris, he was a General Manager in Mettler Toledo's Automated Chemistry Group, starting up and leading a 50-strong team in design and manufacturing of automated drug synthesis equipment. He worked in technical consulting at The Technology Partnership and PA Technology, and in helicopter rotor design at Westland Helicopters. Mr. Gray holds an MA in Engineering from the University of Cambridge, UK, and a Diploma in Management Studies.

Dr. Pavel Abdulkin is an experienced chemist and brand manager, and Head of Particle Works, a sister brand of Dolomite Microfluidics. He earned his Master's degree and Doctorate from the University of Cambridge, UK, where he specialized in the development of novel methodologies for nanoparticle synthesis. After completing his research, he worked as a consultant in the printed electronics industry and co-founded an engineering company specializing in mobile continuous flow platforms for the disposal of liquid rocket fuel. In his current position, he is responsible for developing and implementing the group's strategy, as well as managing the chemistry team and overseeing all chemistry R&D activity.

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PERSONALIZED IMMUNOTHERAPY

Off-the-Shelf Personalized Immunotherapy for Breast Cancer: The BriaCell Solution

By: William V. Williams, MD, Markus Lacher, PhD, and Charles L. Wiseman, MD

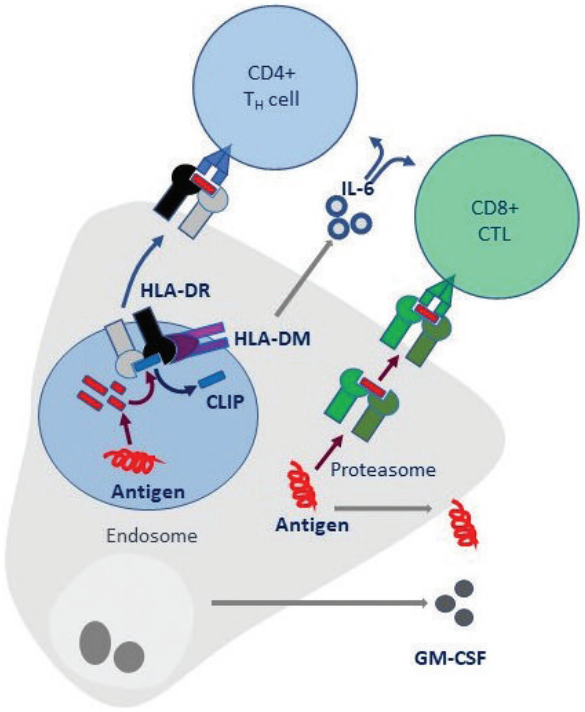
INTRODUCTION

Immunotherapy has taken the oncology field by storm. Several approved drugs, such as the "checkpoint inhibitors" Keytruda® and Opdivo®, have revolutionized the treatment of some cancers. Checkpoint inhibitors work by interfering with immune-suppressive processes, essentially "taking the brakes off" the immune response. However, these drugs only work in certain cancers, and even in these cancers, they only work in 20% to 30% of patients. Also, checkpoint inhibitors can provoke strong immune responses against normal cells, causing autoimmune diseases in addition to other drug-related adverse toxicities.

Another approach comes from the group of "personalized" immunotherapies, for example, Provenge and CAR-T, which may be more specific and have demonstrated clinical benefit. Their downside is that they are extremely difficult to make, requiring that each dose be manufactured for each patient, a time-consuming and costly process. Individualized manufacture inevitably makes these therapies extremely expensive and limits the number of patients who can be treated.

Therapeutic cancer vaccine therapy has been a compelling strategy, with demonstrable immune responses against cancer antigens. But to date, their clinical effectiveness remains unestablished, Provenge being the exception. There is a clear need for ways to stimulate effective cancer-specific immune responses while avoiding time-consuming and costly individualized manufacturing.

FIGURE 1



Bria-IMT™ (SV-BR-1-GM) Proposed Mechanisms of Action. Bria-IMT is a breast cancer cell line with features of immune cells. Bria-IMT makes breast cancer-related antigens that can be taken up by the immune system (especially dendritic cells), processed, and presented to T cells. Bria-IMT also secretes GM-CSF, which further activates the dendritic cells to function as potent antigen-presenting cells. Bria-IMT also is thought to be able to directly present breast cancer antigens to T cells, thereby boosting the immune response. This last mechanism may be unique to Bria-IMT.

CELL-BASED CANCER IMMUNOTHERAPY

Current thinking about cancer biology posits that cancer is a clonal population that replicates at least 30 times to be of detectable size, a process requiring at least many months, perhaps years. During that lengthy time of subclinical tumor growth, whatever host immune response that might have been elicited must have been somehow suppressed. In dealing with the cancer patient, the clinician is asking the immune response to eliminate a relatively huge cancer cell population, in spite of the fact that an adequate immune response was suppressed and couldn't develop when the cancer was small or even microscopic. Immunotherapy, to be effective, must counter such suppressive processes. The efficacy of checkpoint inhibitors supports this hypothesis. But if it's possible to neutralize suppression, it still would be important to upregulate the immune response specific for the particular patient's cancer, and definitively reverse this state of tolerance.[1]

Current understanding of immune cytotoxicity favors a process mediated by CD8+ T-lymphocytes, although important contributions by CD4+ lymphocytes, NK cells, antibodies, and other mechanisms are not discounted.[2] Several reports demonstrate up-regulation of tumor-specific cytotoxic T-lymphocytes following targeted immunotherapy; a change that occurs despite the abundance of antigen that must already be circulating in patients with cancer.

The development of an immune response may be amplified by certain cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), which has been used for protecting bone marrow during intense chemotherapy. It is now being studied intensively as a means to support immunotherapy, in particular by using cancer cell lines genetically modified to produce GM-CSF.[3] Transfected cell lines have several important advantages over injections of GM-CSF, especially their local release of GM-CSF at the site of inoculation and the smaller and perhaps more persistent amounts of the cytokine.

At this time, clinical application of GM-CSF-producing cancer cell lines has not been widely successful.[4] Adaptive immunity includes a humoral component (antibodies) and a cellular component. The cellular component can be further divided into HLA Class I restricted CD8+ T cell responses, which includes cytotoxic T lymphocyte (CTL) responses and HLA Class II restricted CD4+ T cell responses, which include helper T cells that act to boost both the humoral and CTL responses. The effectiveness of cell-based cancer immunotherapies likely is dependent on how well these arms of the immune system are activated. Developing a therapy that activates both the cellular and humoral immune responses and that also somehow addresses the patient's particular "restricted" HLA signature may be an effective strategy.

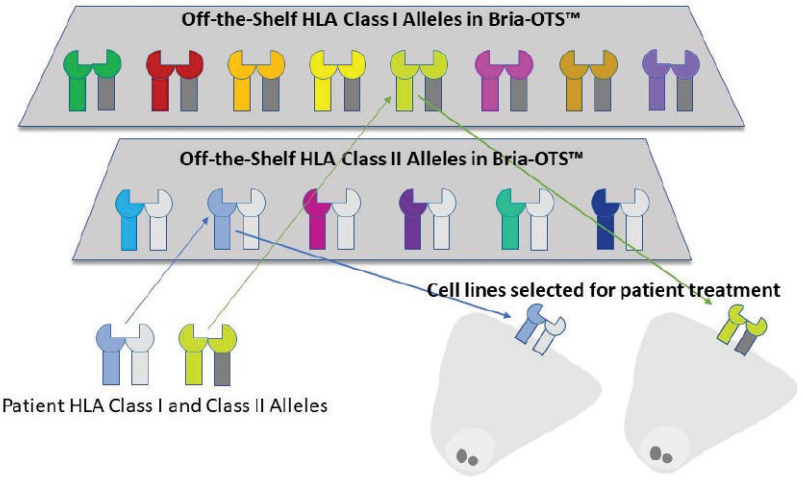
THE BRIACELL STRATEGY

Charles Wiseman, MD, has worked for many years developing and evaluating a variety of cancer cell lines for their efficacy to boost immune responses and hopefully induce clinical improvement. Working first at MD Anderson Hospital in Texas, and then at Saint Vincent's Medical Center in California, Dr. Wiseman used irradiated tumor cell lines to induce anti-tumor immune responses in a variety of cancer patients with some clinical success. Together with Dr. Alex Kharazi, his team developed a breast cancer cell line, SV-BR-1, established from a chest wall lesion of a 36-year-old woman with widely metastatic breast cancer. SV-BR-1 was used in an FDA-approved Phase I trial in subjects with advanced breast cancer, refractory to community-standard chemotherapy. The program utilized both intralymphatic and intradermal routes, and in some cases, using irradiated SV-BR1 admixed with patient peripheral blood lymphocytes. Subjects received low-dose cyclophosphamide prior to inoculation (to reduce immune suppression); GM-CSF (125 µg) was injected subcutaneously concomitantly with SV-BR-1 then repeated daily to total 8 doses. The regimen was administered every 2 weeks for the first month and then once a month. Overall, 54 treatment cycles were administered to the 14 patients (median of 3 cycles with a range of 2 to 7).

The treatment was generally safe and well-tolerated with most adverse events mild, and these consisted principally of erythema and pruritus at the intradermal injection sites. Immune responses were monitored, including evaluation of delayed-type hypersensitivity (DTH) to the irradiated SV-BR-1 cell line (1 million cells intradermally into the forearm) and by looking at antibody responses to the SV-BR-1 cell line using a whole cell ELISA. In the 14 patients, 5 developed a 2x to 4x increase in antibody titer on ELISA. Of 6 patients who had DTH testing pre- and post-dose, 3 had evidence of enhanced cellular immunity following treatment. While none developed an objective response, the mean Kaplan-Meier survival was 17.2 months (median = 9.5 months) at the time of the publication. Six patients survived more than 12 months.[5] The comparable expected survival of patients receiving rescue therapy is usually cited as about 6 to 12 months.

Dr. Wiseman's team then engineered

FIGURE 2



Schematic for the use of Bria-OTS™. Bria-OTS is under development and is proposed to represent a number of cell lines all derived from SV-BR-1, which have been engineered to express a variety of HLA alleles. These cell lines (upper section) would be produced under cGMP conditions and frozen after irradiation for storage. Thus, a patient would present for treatment (lower left) and have HLA typing performed. Once the HLA type is known, the Bria-OTS cell lines would be selected that match the patient's HLA type and shipped directly to the clinical site for patient inoculation. Clinical sites with capability to store cellular products in liquid nitrogen tanks (vapor phase) may stockpile Bria-OTS store and use when needed.

SV-BR-1 to express GM-CSF (now termed SV-BR-1-GM, a.k.a. Bria-IMT™). This transfected line was used in a similar regimen to treat 4 additional patients with advanced cancer. The regimen also included low-dose cyclophosphamide. To challenge multiple lymph node bearing areas, Bria-IMT, 20 million cells, were divided and injected intradermally into 4 sites (right and left shoulder, right and left thigh).

Approximately 2 and 4 days later, interferon alpha-2b (10,000 U) was injected into each inoculation site to further amplify possible responses. As in the prior study, dosing was every 2 weeks for the first month and then monthly up to 5 months (6 cycles).

A particularly remarkable response occurred in a 58-year old woman with metastatic breast cancer initially presenting as superior vena cava syndrome. She was treated initially with doxorubicin and cyclophosphamide and developed a complete remission. Then she was placed on maintenance letrozole while regional irradiation (5800 cGy) was directed to sternal and node-bearing metastatic sites. Nineteen months later, she was noted to have recurrent breast, lung, and other metastases. Letrozole was discontinued. One month later, repeat imaging documented worsening of the pulmonary lesion. The Bria-IMT regimen was started. The protocol allowed a total of 6 cycles over 5 months. Reimaging demonstrated the right breast lesions were markedly diminished, the lung lesions were absent, the right axillary lesions were absent, and the left axillary lesions and the sternal lesions were less prominent. Inoculations were discontinued as required by the protocol.

Approximately 3 months later, PET, CT, and MRI studies identified multiple areas of recurrence in the right breast, several brain metastases, lesions in the lung and mediastinum, and probable liver involvement. Following permission from the FDA, the patient was treated a second time with cycles every 2 weeks. She received a total of 10 cycles and was noted to have marked measurable regression of multiple breast lesions, improvement in the liver and chest lesions, and a complete remission of the multiple central nervous system metastases. Immunologically, the patient was noted to have increased antibody titers to the SV-BR-1 cells and a positive DTH response.[6]

Dr. Markus Lacher, PhD, joined BriaCell in 2015. He asked what differentiated this patient from others, and what characteristics of Bria-IMT could be driving this response. He performed transcriptome profiling on Bria-IMT and HLA typed the patients and the cell line. He noted that the responding patient matched the cell line at HLA-DRB3*02:02, an HLA Class II allele. He further noted that Bria-IMT not only expressed HLA-DRB3 mRNA, but also other molecules needed to present antigens to HLA Class II restricted T cells.[7] Cancer cell lines usually don't express HLA Class II molecules. This characteristic is likely unique and may account for the potency of Bria-IMT, suggesting that Bria-IMT may activate CD4+ cells by virtue of the presence of the Class II HLA allele. The proposed mechanism of action of Bria-IMT is shown in Figure 1. This mechanism has not been demonstrated for other whole-cell immunotherapies and may be key for the Bria-IMT success.

BRIA-IMT™ DEVELOPMENT & TOWARD BRIA-OTS™

Bria-IMT is currently in clinical development for advanced breast cancer. In the first 6 patients accrued, one subject, heavily treated and refractory after receiving 8 different agents, had virtually complete regression of 20 pulmonary lesions 3 months into the program. At 6 months, there was essentially no change, but liver and bone

lesions, stable at 3 months, had then progressed. This response was particularly noteworthy as the patient shares two HLA alleles with Bria-IMT, one Class I and one Class II, a further support to the hypothetical need for HLA matching. Treatment has been generally safe and well tolerated.

In addition to the current clinical work, BriaCell is also now modifying the SV-BR-1 cell line to express additional Class I and II HLA alleles that can then be matched to individual patients. The strategy is shown in Figure 2. Because the cell lines can be frozen in a viable state after irradiation, it will be possible to provide this targeted immunotherapy "off-the-shelf", a personalized immunotherapy without the need for personalized manufacturing.

CONCLUSION

The development of effective targeted immunotherapies is a large unmet medical need. The promising results seen with the whole-cell targeted immunotherapy, Bria-IMT, and the elucidation of the proposed mechanism of action, paves the way for new treatments for breast cancer with potential extension into other tumor types. ◆

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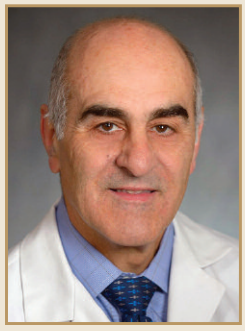
BIOGRAPHIES



Dr. William V. Williams, President and CEO of BriaCell Therapeutics, is a seasoned biopharmaceutical executive with over 35 years of industry and academic expertise, including significant clinical management in multinational pharmaceutical companies. Dr. Williams served as VP of Exploratory Development at Incyte Corporation from 2005-2016. There, he facilitated entry of over 20 compounds into the clinic, including ruxolitinib (Jakafi), baricitinib, and itacitinib. He was responsible for establishing proof-of-concept in several therapeutic areas, and has been involved in numerous new drug applications (NDAs) for therapeutics that achieved marketing authorization in multiple therapeutic areas including oncology. This includes Jakafi for myelofibrosis and polycythemia vera and baricitinib for rheumatoid arthritis.

Dr. Markus Lacher is Senior Director, R&D, at BriaCell Therapeutics, joining the company in July 2015. Previously, he served as a Senior Clinical Scientist, R&D at Cesca Therapeutics, Inc., a clinical-stage autologous cell therapy company, where he played a lead role in the bone marrow transplantation program.

Dr. Charles L. Wiseman is Director of the Board and Co-Founder of BriaCell Therapeutics, bringing more than 40 years of academic and clinical experience to the company. As Co-Founder of BriaCell, he is the inventor for most of the company's intellectual property and actively participates in its ongoing technology development.

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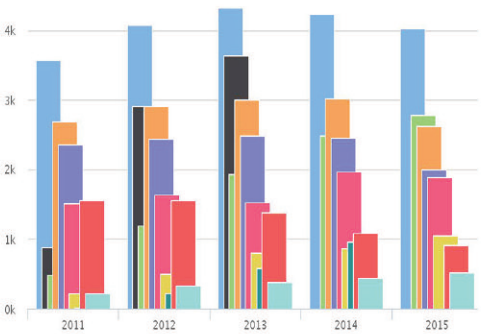

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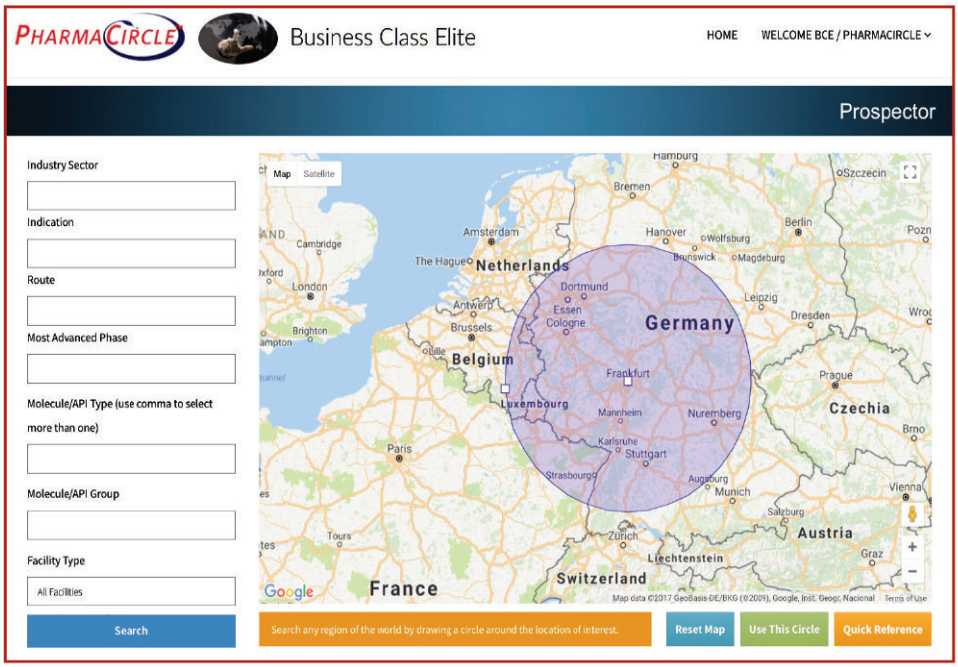

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Special Feature

Outsourcing Formulation Development & Manufacturing: CDMOs Are Innovating for 21st-Century Medicine

By: Cindy H. Dubin, Contributor

Industry insiders say the peak of the patent cliff has passed, and development productivity is increasing, particularly in the areas of personalized medicine, drug delivery platforms, and genome sequencing.

"Historically the pharmaceutical industry worked to meet the needs of individuals who suffer from diseases that impact many millions of people, but development interest is shifting toward more underserved populations of patients who have been diagnosed with rare diseases," says General Manager & Vice President John Rigg at Exelead. "Recent advancements in drug delivery and gene sequencing are major drivers of this trend toward developing such medicines, many of which are good candidates for Orphan Drug status."

But these innovative new therapies require close collaboration and creativity throughout the formulation development process on the part of contract development and manufacturing organizations (CDMOs). "Improving productivity in pharmaceutical development is important but shouldn't come at the expense of creativity," says Dr. Detlev Haack, Head of Research & Development, HERMES PHARMA. "To develop truly innovative products, R&D relies on pharmaceutical developers thinking outside the box. Only with creative people willing to take responsibility for new ideas will we be able to meet the evolving needs of 21st-Century patients and consumers."

In this annual *Drug Development & Delivery* magazine report, some of the industry's leading CDMOs talk about the innovations they are developing for next-generation patient care, and how many are making investments that are enabling them to offer more services under one roof.

Quotient Sciences' spray drying helps to overcome poor drug solubility.

Almac: A Single-Partner Approach Proves Beneficial for a Pediatric Formulation

Almac is a full-service contract development and manufacturing organization that utilizes highly technical core teams capable of developing formulations and analytical methods in-house, then carrying them through to clinical trial material manufacturing, scale-up, commercial manufacturing, packaging, and stability testing.

"Providing both development and commercial operations allows for optimal communication and knowledge transfer on projects," says Cara Young, Director Business Development – Pharmaceutical Development, Almac. "Our clients leverage this integrated service offering, exploiting the advantage of a single-partner strategic approach. Smoothing transition through the drug development process – and ultimately commercialization – saves time, transfers, and other uncertainties inherent in a multi-supplier, multi-site process."

Last year, Almac expanded its GMP manufacturing capacity for solid oral dosage forms and is currently operating from two UK sites, which offer dedicated high-potency processing suites, Gerteis roller compactors, mini-tablets, and stick packs. Almac also established a non-GMP facility to accelerate the formulation development process and facilitate seamless transfer to its GMP facilities.

Within solid oral dose development, Ms. Young says Almac has seen an increased interest in pediatric formulations, highly potent compounds, and small batch sizes. "The increased interest in pediatric formulations is driving a demand for powder-in-bottle, mini-tablets, and stick packs."

She describes one client with a commercialized adult dosage form that needed a corresponding pediatric dosage form with an easy-to-use packaging format. Mini-tablets filled into stick packs were identified as the best presentation. She says Almac successfully optimized several equipment features: Punch tip concavity; ejection scraper design; ejection cam position; and punch and turret keyways. Also designed were 37-tip punches that allowed compression rates up to 550,000 mini-tablets per hour. "And, in conjunction with a third-party specialty vendor, the team successfully identified, installed, and qualified stick pack filling equipment that could operate at up to 80 cycles per minute," says Ms. Young.

AMRI: Core Competencies Span Pre-formulation to cGMP Manufacturing

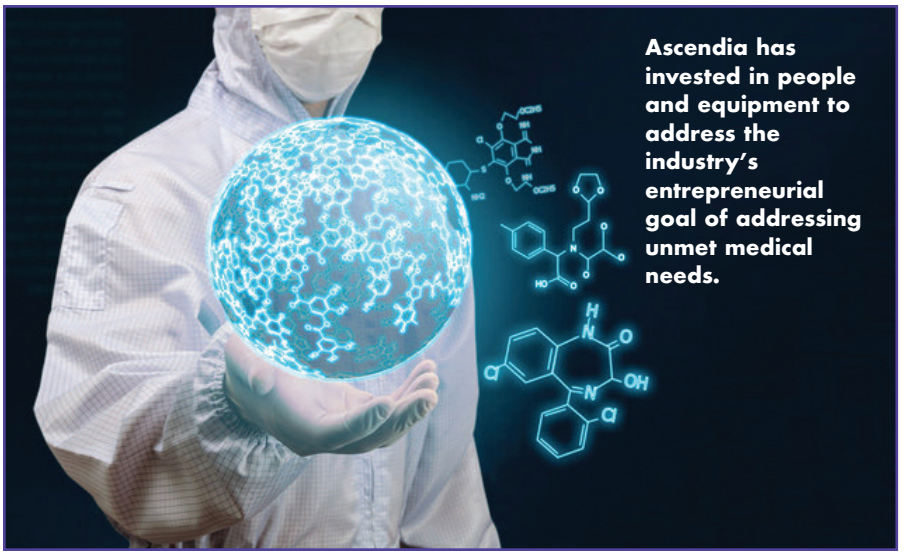
As the market for complex products and biologics continues to grow, biopharmaceutical companies are working with CMO providers who take a more sophisticated approach to sterile dosage form development and manufacturing. AMRI offers formulation development, scale-up, and cGMP supply for liquid and lyophilized products, providing solutions for both simple and complex formulations.

AMRI's expertise in challenging formulations, processes, and approaches includes Tangential Flow Filtration (TFF), extrusion, microfluidization, as well as expertise with viscous products. "TFF requires advanced process knowledge with specific consideration of scale-up to ensure clean execution with complex formulations," explains David Stevens, Senior Vice President, Head of Drug Product, AMRI. "In collaboration with a customer and TFF technology vendor, AMRI supported the successful transfer and scale-up of a peptide formulation, translating data derived from milliliter scale studies to final drug product. Through careful consideration of product and process critical parameters attributes, a bespoke, high-pressure, semi-automated skid was jointly designed enabling a single-step scale-up process with concomitant time and cost benefits."

Additionally, there is growing interest in assessing more complex liposomal or nanoparticulate products at early-stage development to address inherent formulation challenges. Mr. Stevens says the goal is not only to screen potential formulation options, but also for parallel assessment of manufacturing methods viable for scale-up and GMP batch manufacture. AMRI is working in collaboration with a customer, a vendor, and a local university to establish a robust development approach to manufacture liposomal formulations.

"Generally, traditional small-scale manufacturing methods used at the screening stage are impractical for GMP and often present some form of scale-up issue, insufficient process control, or prohibitive cost," says Mr. Stevens. "Our approach focuses on the use of microfluidic technology that permits high throughput, reproducible screening activities, and could be readily scaled up without the loss of product characteristics or introduction of additional process parameters. The academic partnership combines expertise/competencies in liposomal formulation development techniques and parenteral drug product manufacturing to provide an efficient, data-driven route through development to clinical batch manufacture."

Alongside increases in development productivity and customer interest toward biologics, controlled substances, and complex compounds, AMRI has expanded and enhanced operations to support the growing demand for sterile capabilities, such as



Ascendia has invested in people and equipment to address the industry's entrepreneurial goal of addressing unmet medical needs.

the launch of a new, state-of-the-art, aseptic API line in Valladolid, Spain. "Sterile API is a requirement for many parenteral product types, including suspensions and ophthalmics," says Mr. Stevens. "The manufacture of these product types can be provided by AMRI's Drug Product business, which has capabilities in sterile suspensions."

Ascendia Pharmaceuticals: Keeping Pace With Evolving Industry

As a speciality contract development and manufacturing (CDMO) company, Ascendia Pharmaceuticals has witnessed a growing diversity in the types of projects being requested. "In the past, it was common for the majority of projects to be orally administered small-molecule products, often controlled release in some fashion," explains Jingjun "Jim" Huang, PhD, CEO, Ascendia Pharmaceuticals. "Lately, however, we have worked on projects that include peptide delivery (oral and injectable), animal health formulations, long-acting injectable depots, ophthalmic dosage forms (both drops, and vitreal injections), and several device/drug combination products."

Ascendia has positioned itself accordingly by hiring graduate-level scientists with broad backgrounds in new technology and investing significantly in new equipment to handle the broad needs of these programs. "There is tremendous creativity in our field, with numerous entrepreneurial companies looking to develop pharmaceutical products to address very specific unmet medical needs," he says.

When Ascendia was first established in 2012, the company's primary mission was to offer a complete suite of formulation capabilities for early-stage projects to improve a drug's bioavailability. As these early-stage projects are often intended for proof-of-concept, the work needs to be done rapidly and within a set budget. In such cases, Ascendia offer a fixed-fee program with a defined set of deliverables. "Our clients can go from pre-formulation to *in vivo* proof-of-concept relatively quickly and with a known expense, which is beneficial for making efficient decisions on the viability of an early-stage drug program," says Dr. Huang.

Ascendia's mission has evolved to offer cGMP manufacturing services for Phase I and Phase II clinical studies. The company moved into a new facility last year with state-of-the-art manufacturing suites for both oral and injectable products. "This capability expands the cost savings a partner can achieve by working with Ascendia," he says. "A one-stop-shop approach saves time and money as pre-clinical projects can seamlessly transition to clinical go/no-go decision points."

For example, Ascendia developed an injectable nanoemulsion formulation for one client's re-purposed drug. The compound was known to be poorly water soluble, and the current formulation was not suitable for the new indication. "We investigated several formulation approaches before selecting and optimizing a formulation based on stability and solubility data," Dr. Huang explains. "Next, we were quickly able to manufacture small-scale Phase I cGMP CTM for a proof-of-concept bioavailability study. Thus, the client went from a product concept to clinical proof-of-concept in about one year. This is a very efficient way to develop portfolio assets to determine which merit greater expenditure of development resources."

Aztech Sciences Inc.: Focused Protocols for More Efficient Formulation Development

There is great interest in specialized formulation platforms in support of both new drug applications and lifecycle management opportunities, including the 505 B2 pathways, whether it involves small molecules in simple solution vehicle preparations or complex macromolecules in nanoparticle carrier systems.

"Many of our customers are interested in pursuing specialized formulations such as nanoparticle/sub-micron platforms and solution-based vehicles for IV and intranasal applications, among others," says Alphonso Higuera, PhD, Vice President/Co-founder, Aztech Sciences Inc. "For example, our high-shear mixing homogenization

Aztech Sciences Inc. implements a parallel approach during analytical and formulation development to communicate project updates with its clients.

capabilities have provided high dosing formulation vehicles suitable for early-stage/proof-of-concept or IND enabling studies. These platforms, along with traditional suspensions and solid dosage forms, have been of great interest and demand across many of our clients' projects."

As an outsourcing formulation development organization, Aztech implements risk management concepts and Quality-by-Design approaches in its protocols to provide a more focused and efficient pathway in formulation development. This, says Dr. Higuera, leads to more quality and robust formulation platforms, increases productivity, and establishes a template for future project opportunities.

Dr. Higuera adds that Aztech works closely with its clients to ensure that contract development services and deliverables are in full synergy with customers' expectations and objectives. As an example, Aztech developed an intranasal formulation for an upcoming start-up pharma organization with an aggressive timeline to meet an IND-enabling *in vivo* dosing program. To meet the client's expectations and milestones, Aztech implemented a parallel approach during the analytical and formulation development in an effort to provide full transparency and project updates. "The outcome of this approach led to a successful and robust formulation dosing platform in support of the required preclinical studies," he says. "This enabled our client to build a practical perspective and properly align *in vivo* dosing requirements with a third-party animal testing CRO in a timely and efficient manner."

BASF Corp.: Excipients for Challenging Formulations

With continued interest to expedite drug development, the industry is taking more holistic approaches to evaluate novel excipients, such as new polymers and solubilizers, to meet unmet customer needs. Aiming to bring drugs to market faster, the pharma industry is finding more value in high functionality excipients either co-processed, or standalone as a new polymer/copolymer.

"BASF offers technical know-how in the areas of solubilization, instant- and modified-release, soft gel, and skin delivery," says Shaukat Ali, PhD, Technical Support Manager, Pharma Solutions, BASF Corporation. "BASF's partnerships with CROs and CMOs and equipment manufacturers provide insights that allow us to stay ahead of emerging formulation challenges and share knowledge about excipients and their cross-functional uses in oral, parenteral or topical formulations. For example, with our expertise and technical resources in instant- and modified-release, we collaborate with industry to develop coatings, ODT, multi-particulate systems, and taste-masking ingredients for solid oral dosage forms. In the area of polymer chemistry, we are creating new excipients to overcome the challenges with poorly soluble molecules and improve solubility and bioavailability," says Dr. Ali. BASF's alliances with CROs and CMOs have fostered projects with small and large companies focused on traditional oral and topical formulations, as well as on biologics manufacturers and parenteral formulators.

In addition to improving solubility, Dr. Ali says that excipients play an important role in the development of controlled-release dosages. "Life cycle management has been

In the area of polymer chemistry, BASF is creating new excipients to tackle the challenges with poorly soluble molecules to improve solubility and bioavailability.

a subject of continued focus in the industry. For example, developing a once-a-day controlled-release dosage to improve patient compliance is a strategy to extend the life cycle of a drug," says Dr. Ali.

BASF is working with drug manufacturers by supporting their innovation with controlled- and modified-release polymers, peroxide-free binders, and taste masking ingredients, among others. As a result, excipients like Kollidon SR and Kollicoat SR30D and enteric polymers, Kollicoat MAE 30 DP, 100P and 100-55 have been used in many approved drugs with modified-release characteristics. Others such as Kollicoat Smartseal 30DP have been used successfully for taste masking of bitter APIs, and Kollicoat IR has become a standard for controlling the degradation of peroxide-sensitive APIs.

Baxter BioPharma Solutions: Analytical Development Geared to Large Molecules

In Baxter's Bloomington, IN facility, approximately 80% of Baxter BioPharma Solutions' projects involve biologics and the remaining are typically small molecules that require a solubility enhancer such as an organic co-solvent. Baxter's R&D team works with clients to help collaborate on their development needs. "We prefer early involvement from our colleagues in technical transfer and manufacturing, which helps ensure the formulation and process are developed with consideration of the performance at full-scale, and it also ensures that there is sufficient time to purchase new equipment that may be needed to support the project," says Gregory A. Sacha, PhD, Senior Research Scientist at Baxter.

Many new, large molecules are for products that are no longer under patent protection. Baxter BioPharma Solutions' R&D facility in Bloomington is fully equipped with analytical instruments specific to large molecules. These include size exclusion chromatography, imaged capillary electrophoresis, and mass spectrometry. "We have continued to develop our analytical capabilities through the addition of hydrogen deuterium exchange combined with mass spectrometry, the measurement of the unfolding temperature (Tm) using nano differential scanning calorimetry, and analysis of secondary structure using second derivative FTIR," explains Dr. Sacha. "Expansion of the analytical capabilities improves our ability to detect changes in the molecule that may have resulted from formulation excipients or processing techniques, and identifying changes early helps to reduce development time to meet or exceed market demand."

One of the biggest problems in the manufacturing of large-molecule therapeutic agents is the instability of these molecules in aqueous solution, and the need to freeze-dry the drug product to ensure an adequate shelf life. "Freeze-drying is time consuming and inefficient, and this problem has been exacerbated by the traditional trial-and-error approach to the establishment of suitable processing conditions," says Steven L. Nail, PhD, Principal Scientist, Baxter. In this empirical approach, a set of process conditions that provide a pharmaceutically acceptable product is identified, followed by the establishment of "proven acceptable ranges" for process variables, such as shelf temperature and chamber pressure during primary drying. The problem with this approach, says Dr. Nail, is that it provides no information as to whether these process conditions are optimal (meaning that they allow the process to be carried out in the shortest time while still providing a pharmaceutically acceptable product). These edges of failure can be either associated with the product, which would carry a high risk of providing an unacceptable product, or with the equipment, as there is always a limit as to the maximum sublimation rate that a given freeze dryer can support.

"We developed a graphical design space approach, which is basically a map of all the process conditions that result in an acceptable product and this map includes the edges of failure," he says. "The highest sublimation rate within this acceptable range is then, by definition, an optimized cycle. We have applied this approach to numerous client projects."

Catalent: Investing & Acquiring Expertise to Support Customers

Poorly soluble small molecules remain prevalent in pipelines, and the need for bioavailability-enhancing formulations continues to rise. Properly addressing issues at an early stage of development can help prevent failures due to a lack of efficacy caused by poor bioavailability, when the dose is subsequently scaled. In recognition of the growing need to overcome solubility and bioavailability issues, Catalent acquired micronization and spray drying capabilities, and also developed its own facilities and expertise in hot melt extrusion (HME), and has continued to invest in lipid-based delivery.

In April 2018, Catalent announced it will invest $5 million at its Somerset, NJ facility to focus the site on preclinical to clinical Phase 2b formulation, analytical, and manufacturing solutions for orally delivered small molecules. "The additional investment will enable greater speed, flexibility, formulation expertise, and ca-

Catalent's Zydis® orally disintegrating tablets being filled; the technology allows the loading of an API onto a tablet that disperses within the mouth in as little as three seconds.

pacity for early-phase development, and focused capabilities to meet the increased needs of virtual and small pharma companies," says Ronak Savla, Scientific Affairs Manager, Catalent Pharma Solutions.

This is especially critical to serve the needs of biologics companies. To that end, Catalent has acquired the experience and expertise of Cook Pharmica LLC's Bloomington, IN-based business, and has also invested in Catalent's Madison, WI facility to accommodate two, 2,000 liter single-use bioreactor systems. This allows the site to support late-phase clinical and commercial production of up to 4,000-liter batches, and there has also been investment to expand its analytical and process development laboratories at the site. "These investments will strengthen Catalent's position as a leader in biologics development and analytical services, as well as manufacturing and fill-finish," says Dr. Savla.

For example, Neftali Tosado, Director of Continuous Improvement and Technology, Catalent Pharma Solutions, describes how Catalent received a request to fill a unique softgel capsule with 40mg ± 0.9mg API in addition to keeping the existing range of 460–5,000mg with no adverse impact to current overall equipment effectiveness, changeover, throughput, cycle time, etc., and minimal or no regulatory impact. "At the time, it was virtually impossible to fill a softgel with a specific gravity of the paste-like material specified," he says.

Some limits and boundaries for a filling application included: fluid dynamics (e.g., cavitation); injection-timing (e.g., synchronization); product-specific challenges (e.g., suspensions, and non-Newtonian fluids) and; process-specific challenges (e.g., aseptic, high-speed filling). Catalent developed a modular/flexible GMP-compliant API pump technology that covered the full range. In its first attempts with the pilot pump system, the team determined that a small target drift was causing some challenges with the softgels. Catalent eventually stabilized the process so that no drift occurred with the new manufacturing technology. The firm achieved its goal at capabilities of 6-sigma or better across the full range and product viscosities, including many paste-liked materials. "Catalent maintained equal or better efficiencies, reduced changeover cycle times, and improved yields," says Mr. Tosado. "The deployment plan for the new medicine pump filling technology will eventually reach our other sites across the globe."

Although the preliminary development was for softgels, the Catalent team determined that the pump technology was also suited for blow/fill/seal applications.

CPL: Early Development & Commercial Scale-up Under One Roof

CPL focuses on non-sterile liquid and topical semi-solid pharmaceutical products. With these dosage forms, CPL is seeing a trend towards smaller commercial batch sizes with an increasing number of formulations intended for orphan indications. Additionally, companies are incorporating poorly water-soluble APIs into formulations that require high solvent content. This creates a formulation challenge of providing sufficient solubility while ensuring good sensory characteristics for a high level of patient acceptability.

Conrad Winters, PhD, Director, Product Development, says that CPL provides both early product formulation development and commercial manufacturing under one roof. "This has two main benefits for our customers," Dr. Winters says. "The development team designs practical formulations using process conditions that will work at commercial scale and there is no technology transfer between development and commercial – just a seamless integrated process that ensures Right First Time. By having a view toward scale-up and commercial parameters for a product, we can often avoid issues during formulation that may create obstacles or challenges at commercial scale."

To address both new development projects and commercial capacity, CPL re-

Lab-scale mixing equipment in CPL's product development lab.

cently installed innovative manufacturing and packaging equipment that provides flexibility for customers and new formulations. For product scale-up and commercial bulk manufacturing, twin XP Symex vessels with 1000L and 2000L working capacity support clinical and commercial batches 200kg through 2000kg in scalable matched vessels. And for the product packaging operation, CPL invested in two new serialization-ready filling/packaging lines: an XP-rated high-speed aluminum/laminate tube line and a high-speed XP bottle/capping line. "Each line has higher filling speeds to allow for more efficient product packaging while ensuring compliance with regulatory requirements" says Dr. Winters. "These lines will add additional capacity and flexibility to meet future demand, as well as support unique tube and bottle packaging formats.

Evonik Health Care: Demand for Specialized Parenteral Dosage Forms Sparks Facility Expansion

As a CDMO with backward integration in the design and production of functional excipients like EUDRAGIT® and RESOMER®, Evonik Health Care has been helping customers transform their APIs into high-performance medicines for many decades. In addition, the CDMO provides comprehensive support throughout the design, development, production, and scale-up of the finished dosage form. "This combination of products, drug delivery technologies, and value-added services helps customers reduce project complexity, accelerate speed to market, improve drug effectiveness, and strengthen global security of supply," says Dr. Thomas Riermeier, Vice President, Head of Pharma Polymers & Services, Evonik Health Care.

Over the last year, Evonik has seen strong demand for specialized parenteral dosage forms, such as injectable microparticles and lipid nanoparticles. Microsphere formulations can be precisely tuned to control drug release over several weeks or months, based upon the design and choice of polymer, the morphology of the particle, and the process parameters for manufacturing. Lipid nanoparticles have experienced a significant resurgence as well, and they are becoming the de-facto standard for the delivery of genetic-based drugs.

Innovations in such formulations, as well as drug delivery platforms, information technology, and personalized medicine require close collaborations throughout the formulation development process. To support customer projects, Evonik operates a global network of formulation and application labs across the world, including Germany, the US, Japan and India. "These facilities give customers close proximity to our teams of pharmacists, scientists, and engineers who have deep technical expertise in the design and production of polymers, formulations, and finished dosage forms," he says. Evonik also added new platforms and processing capabilities, such as 3D printing, which are helping to change the way drugs are produced. "Such advanced technologies

Evonik Birmingham Laboratories in Alabama is a global center of excellence for biomaterials and the development of polymer-based injectable dosage forms.

will help clear the path for the development and commercialization of a new generation of personalized medicines."

Evonik is also expanding its CDMO and excipient production capabilities in North America to meet growing demand for advanced formulations. This includes a new production facility for its RESOMER polymers, a custom-designed filling line for complex injectable products, and the doubling of its footprint in Vancouver to develop lipid nanoparticle products. In parallel, Evonik is expanding its CMO capabilities for API and advanced intermediates, with a focus on advanced technologies such as continuous processes, fermentation, mPEGs, and HPAPI.

Exelead: Specializing in LNP Delivery

Exelead's General Manager & Vice President John Rigg says there is a resurgence in the development and application of Lipid Nanoparticles (LNPs). As a drug delivery system, LNPs are being used more readily to deliver medicines in which the payload could be a protein, small molecule, large molecule, oligonucleotide (DNA/RNA), or some combination of the aforementioned. "Exciting developments are surfacing around the conjugation of lipids and the integration of different forms of oligonucleotides into LNPs," says Mr. Rigg. "These components are providing the potential to treat and cure the previously untreatable and incurable. Patient-specific (personalized) drugs are rapidly changing the landscape of development pipelines across the entire industry."

Exelead manufactures products in a completely sterile (aseptic) envelope as well as in non-aseptic environments because engineering controls have been built into the system downstream to remove any microorganisms that may contaminate the product. This is all done prior to filling into a vial by passing the finished bulk formulation through a sterilizing grade filter. However, if this form of filtration is used, the particle size is of extreme importance and must be controlled. If the LNPs are too large, they will not pass through the filter, and the product cannot be filled. "As experts in LNP formulation, we have experience in optimizing processes to control particle size to modify established formulation processes to produce aseptic, injectable drug products,"says Mr. Rigg.

As a CDMO, Exelead places an emphasis on complex liposomal and PEGylated formulations, developing and manufacturing batch formulations for the treatment of rare diseases and small patient populations. Exelead recently expanded its formulation and analytical development capabilities to support clients as they develop drugs for unique subsets of the population. This brings new challenges that require manufacturing flexibility, strong intercompany communication, and management of the supply chain. "For instance, personalized medicine doesn't leave a lot of time from once the oligonucleotide is sequenced (or about to be sequenced) to the time that the product needs to be formulated into an LNP at our site," says Mr. Rigg. "These real-time forecasts that only leave weeks to manufacture and release the next clinical batch present challenges that we have been able to overcome with refinement of our existing systems along with the implementation of the new."

Personalized medicine means smaller batches. Thus, Exelead is investing in a multi-million capital expansion project to increase development, formulation, and aseptic fill capacity. The new areas are expected to be ready for use late next year. "We currently support small- to medium-sized batches, and have positioned ourselves to manufacture a parenteral drug product that can range from batch sizes as low as 200 vials to tens of thousands," says Mr. Rigg. "This correlates with formulation batch volumes from well less than 1 liter to as high as 1,200 liters. As this niche market of orphan drugs and personalized medicine continues to grow, Exelead will also continue to grow and partner with new and existing clients to meet this demand."

Halo Pharma: A CDMO for Complex Dosage Forms

Halo Pharma has seen an increase in the number of pharmaceutical companies looking for ways to repurpose APIs through the development of fixed-dose combination products, says CEO Lee Karras. Halo is also experiencing more requests for pediatric dosage form development for branded product label expansions, as well as topical products in both the branded and generic spaces.

In fact, the Generic Drug User Fee Act (GDUFA) is resulting in generics being approved in shorter periods of time, resulting in an increase in generic drug development. "Halo Pharma's product development expertise, coupled with its proven international regulatory track record, has helped the company develop ongoing business relationships with the top-five global generic companies," says Mr. Karras.

Comfortable tackling complex formulation development and manufacturing challenges, Mr. Karras says that Halo Pharma has adopted a synergistic approach with its sponsor customers. "We have a partnering business model that in

Halo's sterile semi-solid suite in Whippany, NJ uses a IWK TZ104 tube handler.

certain situations goes beyond a typical customer/supplier relationship, whereby Halo shares some risk in the development but also some upside when products are ultimately commercialized."

Halo Pharma's comprehensive and collaborative approach to outsourcing has generated success for clients with complex challenges. A recent example involved a tablet product that a sponsor had placed at another CDMO. The product was not able to meet its filed hardness specification, so the sponsor asked Halo to intervene.

"There was a heightened sense of urgency around the product because there was no alternative available and patients needed the product," he says.

Halo Pharma's formulation team, along with pilot plant operators, conducted a series of experiments to determine the cause of the drift in hardness. The issue was ultimately tied back to powder flow, which was modified by changing the way the powder was fed to the press, yet still staying within the filed regulatory requirements of the product.

To support its capabilities around complex dosage forms, Halo Pharma uses complex manufacturing technologies, such as wurster fluid bed coating of beads, extrusion/spheronization, ion-exchange resin formulations, mini-tablet filled capsules, and granule and mini-tablet-filled sachets. Halo's sterile semi-solid suite in Whippany, NJ uses a Krieger 600 MMD batch processor and IWKA TF 20 Robotic Tube Filler, and can manufacture bulk batches from 200 to 450kg, for up to 200,000kg, annually. Halo's non-sterile semi-solid suites utilize a development and pilot-scale Ekato Unimix SRC-150 that can handle batch sizes ranging from 25kg – 150kg. Using this equipment, Halo develops dermatology products such as creams, ointments, and gels. In addition, the production-scale equipment can handle commercial batch sizes up to 1,000kg.

HERMES PHARMA: Focused on User-Centric Products for Modern Patients

HERMES PHARMA has structured its organization to meet the needs of customers, wherever they are in the development pipeline – from idea, through formulation development, to market. The key to developing successful, marketable products is understanding market trends and patient needs. For example, a HERMES business unit manages its own over-the-counter brands primarily for German-speaking markets. "This means we can leverage our understanding of modern patients and markets when working with our customers," says Dr. Detlev Haack, Head of Research & Development, HERMES PHARMA. "It's this wide-ranging expertise that allows us to partner with our customers in different ways, whether that's by co-developing completely new products or via out-licensing one of our pre-existing products."

Recently, one of HERMES PHARMA's customers – a large pharma company – faced the challenge of closing one of its factories. HERMES PHARMA supported them in transferring the manufacture of almost 200 million effervescent tablets, comprising four different formulations (two complete production lines). "Within one year, all of the products were successfully transferred, on time and without any out-of-stock issues," says Dr. Haack. "Moreover, we solved some stability issues, as the products contained moisture-sensitive acetylsalicylic acid as an API. With our specialist TOPO technology and the know-how we've gained over decades of developing and manufacturing water-sensitive effervescent formulations, we were able to improve product quality without changing taste, dissolution properties, or appearance, so that consumers did not observe any changes."

Dr. Haack says that while HERMES PHARMA has placed a particular focus on developing user-centric products, its focus also extends to its packaging. He says: "We continue to develop more user-friendly and environmentally sustainable options. With the new requirements around the Falsified Medicines Directive, we've put considerable investment into

product safety to supply serialized and tamper-evident products. We also continue to expand our plants and invest heavily in the latest high-throughput technologies to ensure we're always able to deliver high-quality products as efficiently as possible for our customers."

Metrics Contract Services: Offering a Concept-to-Commercialization Solution

The Metrics Contract Services business model allows the company to accelerate timelines and deliver clinical trial materials quickly. In fact, Metrics Contract Services has structured itself to facilitate fast-track development by having scientists work in dedicated fast-track suites, conducting product development and manufacturing on a pilot scale outside GMP manufacturing, but with equipment scalable to GMP suites. Additionally, the company offers fast-track analytical testing – delivering same-day testing of prototypes to provide data to its scientists.

In addition to speed, Metrics Contract Services is interested in delivering convenience. The parent company of Metrics Contract Services, Mayne Pharma, recently opened an $80 million, 126,000-sq. ft. oral solid-dose commercial manufacturing facility in Greenville, NC. "The new facility positions Metrics Contract Services to offer development clients a comprehensive concept-to-commercialization solution in one contiguous location under one FDA site registration – delivering larger scale and increased capabilities for seamless scale-up, and reducing or eliminating the need for site transfers," says Yogesh Sadhale, PhD, Associate Director of Pharmaceutical Development, Metrics Contract Services. And with commercial manufacturing housed in the new facility, Mayne Pharma's former manufacturing facility is being repurposed to expand Metrics Contract Services and its pre-commercial product development capacity – creating 10-plus new processing rooms and laboratories.

Scientists at Metrics Contract Services recently were tasked with reformulating a tablet manufactured using a roller-compaction process in a Phase II clinical trial. The original formulation showed high levels of a particular impurity. "After ruling out various possible reasons for the high levels of the impurity, we went back to the beginning, which included revisiting an excipient compatibility study performed by a third party," Dr. Sadhale explains. "One of the excipients in the original formulation, Crospovidone XL, was reported to physically bind to the API, which indicated a potential incompatibility."

Scientists at Metrics initiated tablet reformulation studies, and evaluated a capsule formulation used in a previous Phase I clinical trial. Further reformulation trials revealed that there was likely some interaction between lactose and Crospovidone in the formulation, in addition to a possible effect of pressure, either compaction and/or compression.

"We reformulated the tablet using microcrystalline cellulose and croscarmellose sodium, which resulted in a significant decrease in the impurity level," he says. Additional work is ongoing to evaluate the effect of compaction/compression pressure and to optimize the dry granulation process to improve granule flow.

Quotient Sciences: Optimizing Formulation & Performance Throughout Development

Quotient Sciences' business model integrates CDMO and CRO activities within one organization. This approach simplifies outsourcing supply chains, accelerates timelines, and makes drug development more cost-efficient, says Dr. Peter Scholes, Chief Operating Officer, Quotient Sciences.

"The pinnacle of such integration is Translational Pharmaceutics®, our unique platform that integrates formulation development, real-time adaptive GMP manufacturing with clinical testing." Dr. Scholes explains that through 14-day "make-test" cycles, drug products are manufactured and dosed before emerging clinical data is used to tailor the drug product to be manufactured for the next cohort or dosing period. Flexibility can be maximized by describing a bracketed formulation "design space" in the regulatory submission, within which dose or functional excipient content can be freely adjusted during study conduct. "This approach is ideally suited to optimize formulation compositions and product performance at all stages of the development lifecycle."

Once a new drug product is identified and developed, Quotient offers flexible and scalable clinical manufacturing for global patient trials. Clinical trial manufacturing can be highly personalized and tailored to meet the needs of the trial, based on patient criteria or recruitment rates. Dr. Scholes says this can be significant with oncology, orphan, or pediatric diseases.

Quotient has invested in both capacity and capability, especially to support poor drug solubility and high potency. "We have full internal capabilities for working with all DCS compounds and we also work with technologies suited to improving

R&D laboratory at UPM Pharmaceuticals, Bristol, TN.

the bioavailability of compounds with dissolution, as well as solubility-limited exposure." For high potency, Quotient has purpose-built suites suitable for handling all molecule types.

As far as organic expansion, Quotient recently completed the acquisition of two CDMOs: UK-based Pharmaterials and US-based QS Pharma, which Dr. Scholes says will strengthen Quotient's service portfolio from preclinical formulation development through to commercial manufacturing.

As an example of an early development program, Dr. Scholes describes a first-in-class antifungal treatment. The drug had low water solubility and utilization of an enabled formulation technology was essential to ensure sufficient oral bioavailability in early clinical studies. In this case study, an early development program was designed to rapidly initiate first-in-human (FIH) evaluation using a spray dispersion-in-bottle formulation before transitioning to a solid oral dosage, confirming tablet performance in healthy volunteers and scaling up the manufacturing process to support a Phase II clinical study in patients.

"By integrated early development activities and applying a real-time drug product manufacturing approach, the FIH study was initiated within 12 weeks of initiating SDD process transfer," he says.

An immediate-release tablet was developed and evaluated in a bridging PK study demonstrating 101% relative bioavailability within 26 weeks of commencement of formulation development. The scale-up of the SDD tablet process and generation of data for inclusion in the regulatory filing to support the Phase II clinical program was completed within a further nine weeks. Overall, the entire early development program, including FIH trial, solid oral dosage form development, and provision of data to initiate a Phase II clinical program was completed in less than 13 months.

UPM Pharmaceuticals: Small CDMO Offers Big CDMO Capabilities

Tablets and capsules remain UPM's primary focus for meeting client needs in these areas, including specialty forms such as ODTs (oral disintegrating tablets), mini-tabs, immediate- and modified-release solutions, and neat API encapsulation. UPM also has extensive expertise in oral peptide development. Changes in 2016, including the implementation of the manufacturing quality assurance (MQA) initiative as well as the realignment of laboratories and specific capabilities, have ensured more efficient production and more consistent operations to achieve faster time to market, even for challenging APIs, explains Hulya Sahin, PhD, Senior Director Product Development, R&D, UPM.

"As a client-focused CDMO, UPM is vested in providing more than just capacity for the production of drug products on a fee-for-service basis," says Dr. Sahin. "We don't own our own products or any proprietary technology, but we are open to working with a client's technology, dedicating space and capital investments for a solid partnership."

In addition, UPM's R&D group works with a deliverables-driven system for scheduling, development, and production. "Although a smaller CDMO, UPM offers proof-of-concept services through clinical and commercial manufacturing support – but with the personalized, responsive service of a well-funded, family-owned organization that emphasizes customer service and satisfaction," says Dr. Sahin.

In the last five years, UPM has expanded its facilities from 40,000 sq. ft. to over 750,000 sq. ft., and has grown its employee base from 65 to 265 while modernizing operations. Says Dr. Sahin: "We have greatly invested in capital improvements, including the construction of a state-of-the-art R&D feasibility lab with five processing rooms and scalable equipment that supports our clients from development to commercialization. We have also added a low humidity suite and serialization capabilities." In addition to the capital expenditures, UPM has hired development scientists with backgrounds in formulation development, including modified-release technologies for tablets and capsules, and process development, clinical supplies manufacture, and scale-up and technology transfer. ◆

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MULTIPARTICULATE SYSTEM

Advances in Lipid Multiparticulate Technologies for Controlled Release

By: Jaspreet Arora, PhD, Samantha Saville, and Brett Waybrant, PhD

INTRODUCTION

Multiparticulates (MPs) have been extensively utilized in specialized applications given their dosing flexibility; ability to incorporate modified-release approaches (eg, taste-masking); and safety considerations (eg, guarding against dose-dumping issues versus monolithic formats). The continued move toward more patient-centric medicines is expected to accelerate this trend, given the rising geriatric population and regulatory requirements for specialized pediatric formulations. In addition to addressing the issues facing many compounds today – low aqueous solubility and more specialized target product profiles, formulators must also increasingly consider palatability issues (eg, taste, odor, mouthfeel); ease of administration by caregivers; and dosing flexibility across patient populations and subgroups.

The need for improved drug delivery systems for pediatrics is compelling, given the special formulation needs, safety considerations, and challenges of oral dosing within this patient population. Formulators must factor in a range of special considerations for pediatric patients, in addition to the challenges in formulating medicines for all patient groups, APIs with low aqueous solubility or bitter taste and precise target product profiles for specific drug delivery and safety.[1,2] Pediatric patients often have different physical and metabolic needs from adults, and particular difficulty in swallowing conventional solid oral dosage forms, which can result in patient compliance issues.[3] They also typically require smaller doses of the drug and require more dose flexibility due to a wide range in body weight. Additionally, children are more resistant than adults to palatability issues (eg, objectionable characteristics in terms of taste, smell, or mouthfeel such as slight grittiness). Because pediatric formulations must often be given by adults in constrained situations (eg, around school or daycare schedules), formulations are needed that are easy to administer, while providing for flexible dosing requirements, accommodating complicated drug delivery profiles, and ensuring patient safety and acceptance.[4]

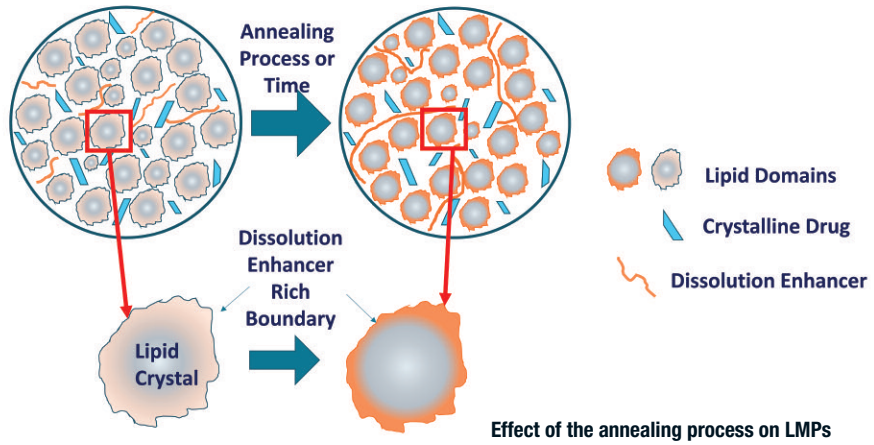
Lipid multiparticulates (LMPs) in particular offer an attractive formulation option for pediatric use. This platform technology has demonstrated efficacy, combining the flexibility and safety aspects of oral multiparticulates, the advantages of lipidic delivery systems, and compatibility with a wide range of convenient delivery systems.[5] LMPs are made by a solvent-free melt-spray-congeal (MSC) process using precedented, lipid-based excipients with good safety profiles. Because LMPs are solid and lipid-based, no preservatives are required to prevent microbial growth. API dissolution rate is controlled by varying excipient composition, making both immediate- and controlled-release formulations achievable.

The following focuses on a controlled-release LMP formulation to identify optimum annealing conditions and to better understand the annealing mechanism. Controlled-release dosage forms for pediatric patients are increasingly needed due to regulatory requirements when controlled-release product enhancements are used for adult products as part of a lifecycle management strategy. Children are not able to swallow controlled-release tablets and therefore require an MP-based dosage form. Annealing addresses an issue that can affect the dissolution performance of controlled-release LMPs after their manufacture. Specifically, we investigated whether annealing could be used to improve the stability of LMPs after congealing, accelerating thermodynamic

forces that can result in phase separation and varying dissolution rates.

LMPs were prepared using an MSC process and characterized after annealing at high temperature and relative humidity (RH). Results showed that annealing could be used to accelerate kinetic transitions of the lipid matrix from high-energy forms (present after manufacture) to lower-energy polymorphs that are thermodynamically more stable. This transition should prevent changes in the dissolution profile of the LMPs after manufacture.

FIGURE 1



Effect of the annealing process on LMPs

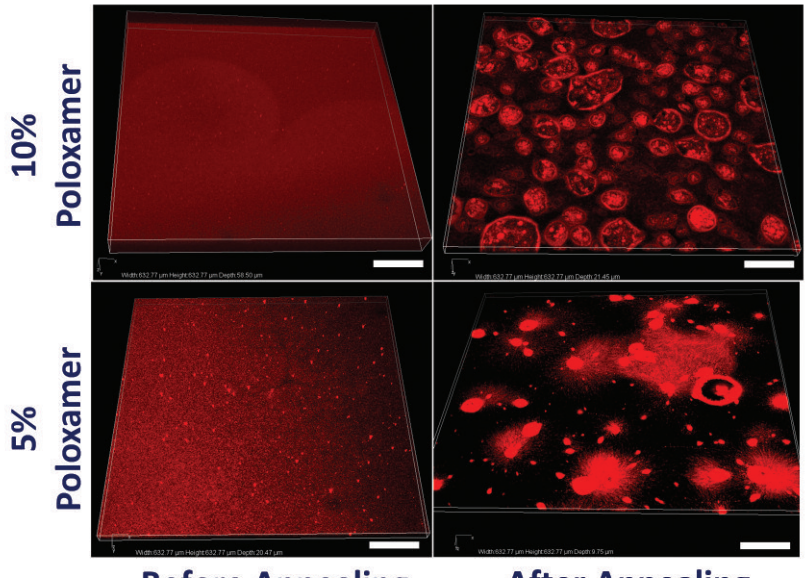
PROCESS DESCRIPTION

This drug delivery platform is based on LMPs manufactured using a proprietary MSC process. In this process, a feed of molten excipients dispersed with crystalline API is prepared and then fed to a rotary spinning-disk atomizer in either a continuous or batch process. The atomizer creates droplets that are then rapidly congealed in a cooling chamber, forming solid LMPs. The LMPs are collected, and for controlled-release formulations, the LMPs are annealed at high temperature and humidity. Immediate-release LMPs are not annealed. The final drug product consists of spherical, smooth lipidic-wax-matrix LMPs, typically 50 µm to 300 µm in diameter, with the API homogenously dispersed throughout.[6]

A primary strength of the MSC process is the flexibility it offers in the production of LMPs with a variety of release rates. Release rates can be tuned by altering the ratio of dissolution enhancer to lipid matrix or using lipids with different hydrophobicities.[2,6] Immediate-release or controlled-release profiles can be achieved without the need for rate-controlling coatings. Modified-release coatings – to achieve taste-masking, enteric protection, or delayed release, for example – can be applied using a standard fluid bed coater to meet the desired release profile. Either coated or uncoated, LMPs are well-suited for use in numerous types of dosage forms, including novel capsules that can be snapped open to sprinkle the contents, sachets, orally disintegrating tablets (ODTs), and liquids, depending on the target product profile.

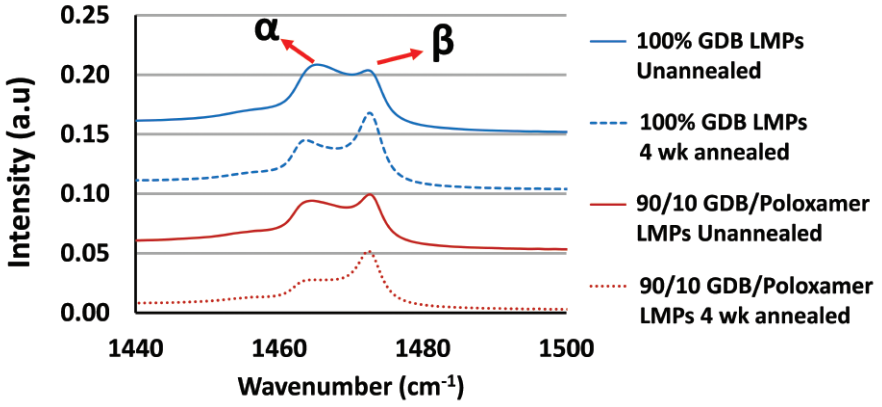
The MSC technology is well-characterized, and critical process parameters have been identified and characterized for each process step, allowing precise control over product characteristics and performance. Rapid congealing promotes excellent encapsulation efficiency and produces easy-to-swallow multiparticulates that have an acceptable mouthfeel for age-appropriate dosing. The technology has established market precedence – for example, Zmax®, a single-dose antibiotic, is marketed by

FIGURE 2



Confocal imaging results for melt-cast films containing 10% and 5% poloxamer before and after annealing for 1 week at 50ºC/75% RH (scale bar = 100 µm)

FIGURE 3



FTIR spectra of LMPs consisting of 100% GDB or containing 10% poloxamer before and after annealing for 4 weeks at 50°C/75% RH

Pfizer Inc.[7]

The nature of the excipients used in controlled-release LMPs warrant annealing. The majority of the LMPs consist of a lipidic wax matrix, and the release profile is adjusted using a dissolution enhancer (ie, a pore former). As the molten feed containing the dispersed crystalline API is atomized by the rotating disk, drops form, which rapidly congeal, encapsulating the crystalline drug in a mixed-phase form of partially crystalline excipients. These excipients are in a high-energy, less stable form because of the rapid congealing and, thus, are thermodynamically driven to change form. Over time, the lipidic wax matrix and dissolution enhancer are susceptible to phase separation and recrystallization of different polymorphs, which can alter the dissolution profile of the API.

Annealing is thought to occur through two primary mechanisms. First, upon rapid congealing, portions of the dissolution enhancer (poloxamer) can become kinetically trapped in the semi-crystalline lipid domains. As the lipid matrix crystallizes during annealing, the dissolution enhancer is excluded from the crystal and is pushed toward the grain boundaries. On annealing, the dissolution enhancer rearranges and forms more organized structures around matrix crystals. This rearrangement forms a porous network of hydrophilic domains that allows water to penetrate the LMP and drug to release.

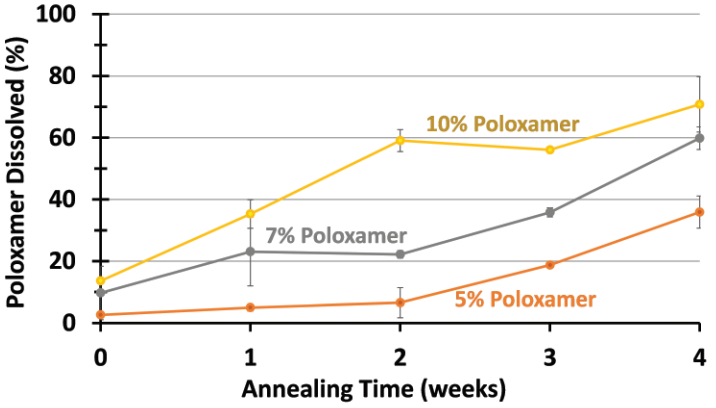
Second, the lipid matrix, glyceryl dibehenate (GDB), almost always exists as a mixture of α (high-energy) and β (denser, more stable) polymorphs. In the rapidly congealed LMP, the α polymorph is predominant. Upon annealing, this polymorph is transformed to the thermodynamically more stable β polymorph. This leads to densification of the lipid matrix, increasing the internal free volume or porosity of the matrix. These two mechanisms cumulatively reduce the effective diffusion path length of the API. These concepts are shown in Figure 1. Drug is released from LMPs when they are wetted with water, hydrating the dissolution enhancer and wetting the drug crystals. The dissolution enhancer and drug then dissolve and diffuse out of the LMPs.[8]

RESULTS

The goal of this study was to investigate how the state and morphology of the lipidic wax matrix changes upon annealing and to evaluate the effect of those changes on the resulting dissolution rate. In-depth knowledge of the annealing process provides an opportunity to minimize the stability risk associated with alteration of the target release rate in LMPs after their manufacture.

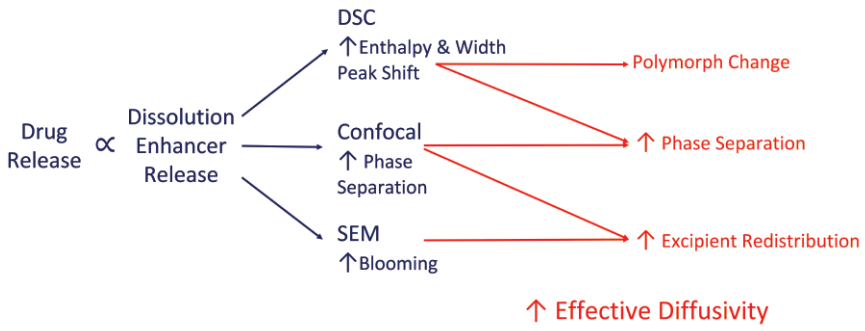
Placebo LMPs and thin films were composed of a lipidic wax matrix (ie, glyceryl dibehenate [GDB], [Compritol® 888 ATO]) and a dissolution enhancer (ie, poloxamer 407, [Kolliphor® P407]) at three poloxamer loadings: 5%, 7%, and 10%. Control LMPs with 100% GDB were also manufactured for physical characterization. The LMPs were prepared using the MSC process by introducing a melt of the

FIGURE 4



Dissolution performance, showing poloxamer dissolved as a function of annealing time for three LMP formulations with various poloxamer contents

FIGURE 5



Summary of characterization results and evidence for physical changes

components onto a spinning disk. The LMPs were sieved to a particle size of 150 µm to 350 µm. Films of GDB and poloxamer labeled with Texas Red dye were fabricated by hot-melt casting. The LMPs and the films were annealed at 50°C/75% RH for up to 4 weeks and characterized before and after annealing using the following techniques: (1) confocal laser microscopy; (2) scanning electron microscopy (SEM); (3) Fourier-transform infrared spectroscopy (FTIR); (4) modulated differential scanning calorimetry (mDSC); and (5) dissolution testing.

Confocal Laser Microscopy Imaging

The goal of these tests was to determine the effect of annealing on phase separation of melt-cast films consisting of GDB and poloxamer. Melt-cast films containing 5% and 10% poloxamer were tested before and after annealing for 1 week. Labeling the poloxamer with the Texas Red dye made it possible to capture the internal rearrangement of the poloxamer after annealing.

As shown in Figure 2, the confocal images of films showed differences in the internal arrangement of poloxamer domains, with much more phase separation and excipient redistribution evident after annealing. This information was important because drug transport occurs via the porous network of the LMPs.[8]

SEM Imaging

The goal of these tests was to determine if annealing produced observable effects on the surface of the LMPs. SEM images were taken before and after annealing of LMPs consisting of 100% GDB or LMPs with poloxamer contents of 5%, 7%, and 10%. SEM images revealed "blooming," a characteristic of fats, on the surface of the LMPs after annealing at all annealing times and poloxamer contents (data not shown). The surface coverage of blooms was greater for LMPs containing poloxamer than for 100% GDB LMPs for similar annealing times.

FTIR Analysis

The goal of these tests was to determine if changes in the proportions of α and β polymorphs of GDB occurred after annealing. LMPs consisting of 100% GDB or containing 10% poloxamer were tested by FTIR before and after annealing for 4 weeks. As Figure 3 shows, the proportion of β polymorph increased with (a) annealing time and (b) with addition of the poloxamer to the formulation.[8]

mDSC Analysis

The goal of these tests was to determine if changes in the thermal characteristics of the LMPs occurred after annealing. LMPs were tested for melting events and the melting-peak characteristics were analyzed. Results showed the enthalpy of fusion of the lipid peak increased with annealing time and that the lipid melt peak widened and increased with annealing time. The increase in melt enthalpy is attributed to formation of the more-stable β polymorph, and peak widening is attributed to existence of multiple polymorphs of GDB (data not shown).

Dissolution Testing

The goal of these tests was to determine if changes in the dissolution performance of the LMPs occurred after annealing. The dissolution performance of LMPs was tested using a standard USP II apparatus in a pH 6.8 phosphate buffer as a function of annealing time for LMP formulations containing 5%, 7%, and 10% poloxamer. As Figure 4 shows, (a) the release rate is tunable by poloxamer content and (b) the dissolution rate changes upon annealing, which should be well characterized.[8]

DISCUSSION

The results summarizing the physical changes that occur with LMP annealing and their effect on dissolution performance are illustrated in Figure 5.[8] These results show that annealing can be used to accelerate kinetic transitions from high-energy polymorphs (present after LMP manufacture) to lower-energy polymorphs that are thermodynamically more stable. This transition should prevent changes in the dissolution profile of the LMPs during storage. Further, the studies showed adjustable drug release can be achieved by varying the ratio of dissolution enhancer to lipid matrix.

This work investigated placebo LMPs (ie, with no API present in the formulation). In formulations with API, the mechanism of

annealing is similar, but the rate of annealing varies. In one example with LMPs with low drug loadings, the drug dissolution rate and the enthalpy of fusion of the lipid melt peak stabilized after annealing for 2 weeks and did not alter upon further annealing (data not shown). Another example of LMPs with moderate to high drug loadings showed shorter annealing times of just a few days (data not shown). We hypothesize that the API, which remains crystalline through the manufacturing process, provides nucleation sites for lipid matrix crystallization, affecting the dissolution enhancer and lipid matrix organization and form. However, the annealing mechanism remains the same. These limited studies have advanced our understanding of the annealing process and its effects on physical and dissolution properties of LMPs and should prove invaluable in choosing the best annealing conditions for future controlled-release LMP formulations.

CONCLUSIONS

In summary, LMPs are a promising technology for specialized formulations, including patient-centric (pediatric and geriatric) drugs that require adjustable-release characteristics. Drug dissolution from LMPs can be modified by varying the loading of dissolution enhancer. Optimal annealing conditions can be chosen to minimize any changes in LMP dissolution rate during storage. Annealing studies can thus be used to mitigate the long-term stability risks of deviating from the target product profile.

ACKNOWLEDGMENTS

We would like to acknowledge Cody Prather, Warren Miller, Amanda Pluntze, Chris Craig, Kathryn Pugh, Matt Shaffer, and Jonathan Cape of Lonza Pharma & Biotech for their work on this. ◆

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BIOGRAPHIES

Dr. Jaspreet Arora, Senior Engineer, Product Development, Lonza Pharma & Biotech, is a chemical engineer focused on multiparticulate drug delivery. Presently, his work focuses on formulation, manufacturing, and analytical characterization of lipid multiparticulates (LMPs) for controlled release.

Samantha Saville, Scientist II, Lonza Pharma & Biotech, is an analytical chemist working with multiparticulate dosage forms for immediate release, modified release, and taste-masking applications. She uses USPII dissolution, assay, related substance, SEM, microtoming, EDS, HPLC, PION, appearance, and stability tests to determine drug availability and taste-masking.

Dr. Brett Waybrant, Product Development Lead, Lonza Pharma & Biotech, is focused on multiparticulates, including lipid multi-particulates (LMPs) manufactured using the melt-spray-congeal (MSC) process and spray layered multiparticulates. His work encompasses formulation, manufacturing, and fluid bed coating of the multiparticulates for taste-masking, enteric protection, modified release, bioavailability enhancement, and pediatric applications.

THERAPEUTIC FOCUS

Antisense Drug Shown to Significantly Reduce Triglyceride Levels in Patients With Severe Hypertriglyceridemia

By: Ioanna Gouni-Berthold, MD

INTRODUCTION

Hypertriglyceridemia can result from an unhealthy lifestyle, obesity, physical inactivity, excessive alcohol intake, metabolic syndrome, type 2 diabetes mellitus, and more rarely from genetic disorders (eg, familial chylomicronemia syndrome, familial partial lipodystrophy, familial combined hyperlipidemia, familial dysbetalipoproteinemia).

Apolipoprotein C-III (apoC-III) is a key modulator of plasma triglyceride (TG) levels. It has been shown that loss of function mutations in apoC-III are associated with lower TG levels and a reduction in cardiovascular risk while elevated TG levels are associated with increased risk of both cardiovascular events and pancreatitis. In recent years, there has been an effort to develop strategies to reduce levels of apoC-III in order to reduce elevated triglyceride levels. Based on this background, our team led a pivotal study in patients with severe hypertriglyceridemia, defined as triglycerides ≥ 500 mg/dL, with volanesorsen, a second-generation antisense oligonucleotide that inhibits apoC-III synthesis. Antisense technology is based on the use of synthetic nucleic acid sequences to interrupt the production of a specified protein by targeting the corresponding messenger RNA, or mRNA, that encodes that protein. Antisense drugs are therefore able to reduce the level of proteins that cause or contribute to the progression of various diseases, including hypertriglyceridemia.

TARGETING LIPID & LIPOPROTEIN RISK FACTORS

Lipid and lipoproteins, including LDL-C, triglycerides, apoC-III, and Lp(a), are associated with development and progression of atherosclerotic cardiovascular diseases. Moreover, increased TG levels are associated with incidents of acute pancreatitis and liver disease such as non-alcoholic steatohepatitis (NASH). The protein apoC-III, the second most abundant lipoprotein, circulates in the bloodstream attached to particles containing triglycerides and inhibits TG-hydrolysis. High levels of apoC-III have been associated with hypertriglyceredemia.

Mutations in the apoC-III gene that impair its function result in lower TG levels and a correlated reduction in cardiovascular risk. Conversely, overexpression of the same gene has been associated with elevated TG levels and increased risk of both cardiovascular events and pancreatitis. In recent years, there has been an effort to develop strategies to reduce levels of apoC-III in order to reduce elevated triglyceride levels.

THE COMPASS STUDY

The COMPASS clinical trial was a randomized, multi-center, double-blind, placebo-controlled, 26-week, Phase 3 study to evaluate the effect of apoC-III reduction with the investigational antisense drug volanesorsen on TG levels in patients with hypertriglyceridemia. The trial included patients with fasting TG ≥ 500 mg/dL, (n=113, mean ±SD, TG level 1261 ±955mg/dL) who were randomized 2:1 on volanesorsen or placebo. Patients

were treated with 300-mg volanesorsen subcutaneously (SC) of placebo once a week for 26 weeks.

Results from the clinical study indicate that antisense technology can result in significant reductions in triglyceride levels in patients with hypertriglyceridemia:

- Patients treated with volanesorsen (n=75) achieved a 71.2% mean reduction in triglycerides after 13 weeks of treatment, compared with a mean reduction of 0.9% in placebo-treated patients (n=38).

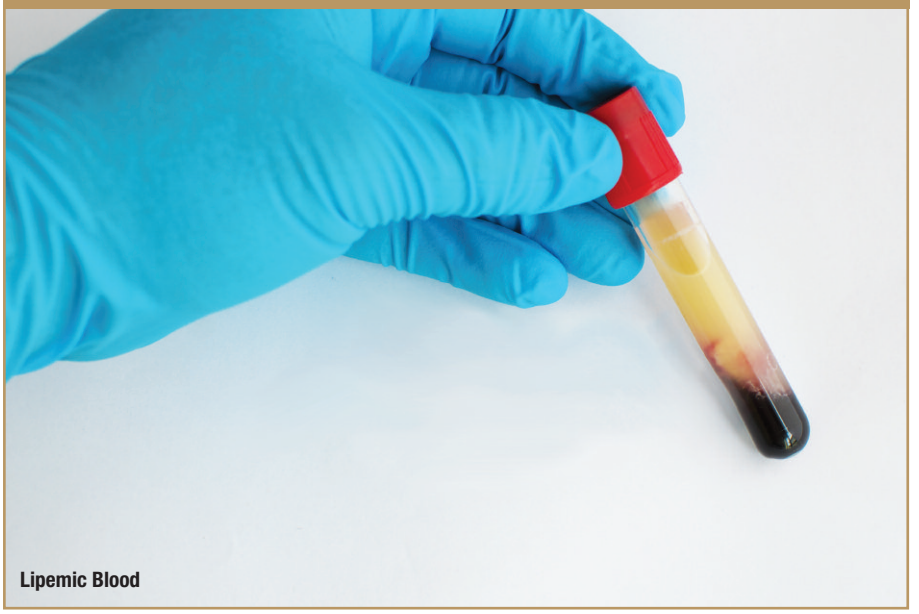
- The treatment group included a subset of patients whose hypertriglyceridemia was associated with familial chylomicronemia syndrome (FCS), a rare, genetic disorder characterized by extremely high levels of triglycerides and risk of recurrent, potentially fatal pancreatitis. People with FCS are unable to effectively clear large, triglyceride-rich lipid particles called chylomicrons due to a deficiency of lipoprotein lipase, an enzyme that helps break down triglycerides. In a subset of seven patients with FCS who had average incoming triglyceride level of 2,280 mg/dL, volanesorsen-treated patients (n=5) achieved a mean reduction in triglycerides of 73% from baseline after 13 weeks of treatment, compared with a mean increase of 70% in placebo-treated patients (n=2).

- Results also showed that 82% of patients treated with volanesorsen, including three of the FCS patients, achieved triglyceride levels less than 500 mg/dl after 13 weeks of treatment, compared to 14% of placebo-treated patients (p<0.0001).

- Patients treated with volanesorsen also had reduced risk of pancreatitis events, with no events reported in the treatment group and five reported in the placebo group.

- The most common adverse event in the volanesorsen-treated group of patients was injection site reactions (ISRs), which were mostly mild. In this study with patients who are largely asymptomatic and, unlike FCS patients, do not need to manage the daily burden and symptoms of their disease, 13% of treated patients discontinued due to ISRs and 7% of treated patients discontinued treatment for other non-serious adverse events. There were no deaths in the study. None of the FCS patients in the study discontinued. In addition, there were no serious platelet events in the study. There was one potentially related SAE on the drug-treated arm. This was a report of serum sickness that occurred two weeks after the last study dose and resolved without treatment, and after thorough investigation the sponsor determined that the case was not likely caused by the drug.

FIGURE 1



Lipemic Blood

The COMPASS study was a supportive study used to further validate findings from the APPROACH study, a randomized, double-blind, Phase 3 study of volanesorsen in the treatment of patients with FCS specifically.

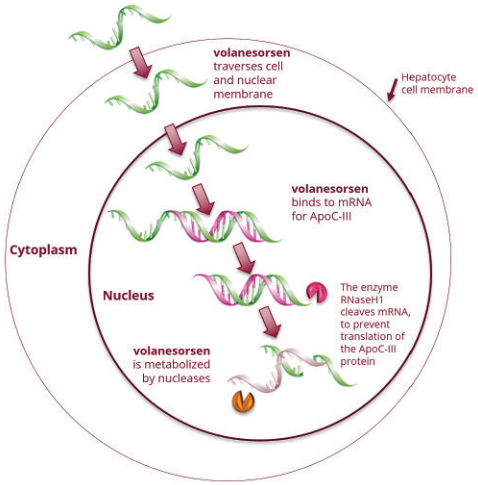
THE APPROACH STUDY

The APPROACH study was a 52-week Phase 3 study in 66 patients with FCS.[1-3] While the enzyme lipoprotein lipase (LPL) normally breaks down chylomicrons, people with FCS do not have functioning LPL, resulting in circulating triglyceride levels in the thousands (mg/dL) or more than 10 times the upper limit of normal.[1-4] FCS patients have a significant risk of morbidity

FIGURE 2

Volanesorsen Mechanism of Action

Preventing Formation of ApoC-III by a Second Generation Antisense Oligonucleotide (ASO)



Attributes of Antisense Drugs

- Highly specific, with reduced potential for off-target binding
- No known drug/drug interactions, not metabolized by CYP450 pathways
- Unable to cross placenta and blood/brain barrier

and mortality, including recurrent episodes of acute pancreatitis, which can be fatal.[5-7]

In the APPROACH study, FCS patients treated with volanesorsen experienced robust reductions in triglycerides and related benefits, including:

- A 77% mean reduction in triglycerides after three months compared to a mean increase of 18% in placebo-treated patients.
- Volanesorsen-treated patients with the highest documented frequency of pancreatitis attacks suffered no attacks during the 52-week treatment period (p=0.02).
- A reduction in abdominal pain was observed in volanesorsen-treated patients compared to placebo-treated patients.

THE IMPACT ON STANDARD OF CARE

Guidelines established by the Endocrine Society suggest dietary counseling and weight loss for the treatment of mild-to-moderate hypertriglyceridemia in patients who are overweight or obese. Patients with more severe forms of hypertriglyceridemia are typically managed with reduced intake of dietary fat and simple carbohydrates in combination with drug therapy including fibrates, nicotinic acid, omega-3 fatty acids or statins, alone or in combination. In many patients, currently available management strategies are unable to normalize triglyceride levels or decrease the risk of pancreatitis.

Current TG-lowering drugs work mainly through the LPL pathway, thus being largely ineffective in patients with FCS.[1,7,8] The results of the COMPASS study provide strong additional support for therapeutic strategies decreasing triglycerides levels by reducing apoC-III concentrations in patients with severe hypertriglyceridemia including the very difficult to treat FCS patient population.◆

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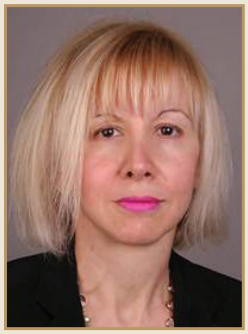
BIOGRAPHY



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CLINICAL TRIALS

Maximizing Immuno-Oncology Clinical Trial Success

By: Luke S. Gill, MSc, MBA

INTRODUCTION

Hailed by many as the future of cancer therapy, immuno-oncology leverages and unleashes the body's immune system to recognize and eliminate cancer cells. Immune checkpoint inhibitors have already revolutionized the treatment of certain solid tumors and hematologic malignancies by acting on pathways that cancers co-opt to evade immune recognition. Now, emerging therapies, such as chimeric antigen receptor T-cells (CAR-T), dendritic cell vaccines, bi-specific T-cell engager (BiTE) antibodies, oncolytic viruses and even gene transfer and gene editing, are pushing the envelope even further.

THE GREAT LEAP FORWARD

Present day advances in immuno-oncology can be attributed to a paradigm shift in our understanding of cancer. Even up to the early 2000s, cancer was considered a disease of genetic origin, characterized by sustained proliferation; resistance to apoptosis; and the ability to promote angiogenesis, invasion, and metastasis. However, this view failed to account for the dynamic nature of the interactions between the tumor and its microenvironment — not just normal surrounding tissue cells, but also the immune system.

Now, we understand that the immune system plays a dual role in cancer, not only protecting the host against tumor formation, but also shaping tumor immunogenicity. This understanding has led to the development and approval of new immunotherapies, heralding a new — and potentially lucrative — era of cancer treatment. Immunotherapy trials now comprise more than one third of the clinical oncology space. In 2016, the cancer immunotherapy market was estimated to be $41 billion, and it is expected to grow to nearly $119 billion by 2025.[1]

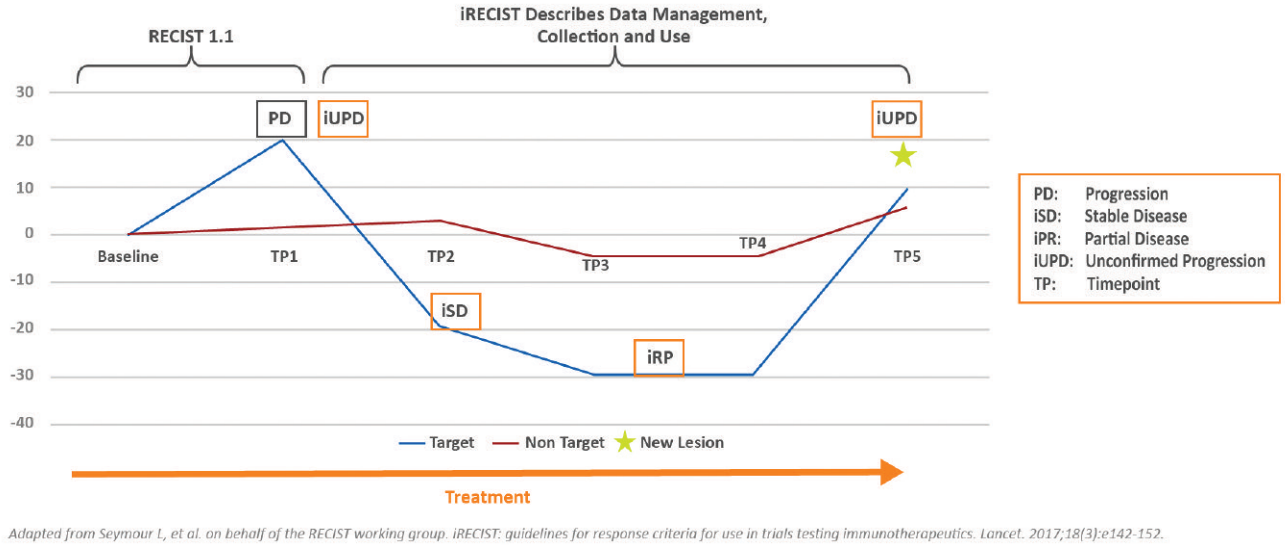
Small biotech and specialty pharma are poised to play a critical role in this growth, but will face challenges that are intrinsic to the development of immunotherapeutic agents. Immunotherapy innovations work differently than cytotoxic chemotherapy, and these differences may impact dosing, response measurement, biomarker validation, selection of combination therapies, and identification of adverse events. Understanding and overcoming these challenges will be critical to clinical trial success and, ultimately, market approval.

DETERMINING THE RIGHT DOSING PROTOCOL

Traditionally, early phase trials in oncology aim to establish the maximum tolerated dose (MTD) for later phase trials. However, immunotherapies can elicit therapeutic responses at doses below where toxicity is seen. Instead, dose-finding for immunotherapies often requires titration to a biologically effective dose, rather than an MTD where toxicity is the limiting factor.

Moreover, when present, toxicities associated with immunotherapies may not be dose dependent. In some cases, such as with CAR-T, toxicity may actually indicate efficacy. As a result, dose-escalation methods with toxicity-based endpoints may be less relevant for immuno-oncology trials and alternative parameters may be more appropriate.

FIGURE 1



Adapted from Seymour L, et al. on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet. 2017;18(3):e142-152.

Assessing Tumor Response Using iRECIST
(Adapted from Seymour L, et al. on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet. 2017;18(3):e142-152.)

MEASURING RESPONSE TO CANCER IMMUNOTHERAPIES

Generally, four distinct response patterns are associated with favorable overall survival:

1. Response in baseline lesions (ie, a typical RECIST response)
2. Stable disease with slow decline in tumor volume
3. Response following an initial increase in tumor volume
4. Response following the appearance of new lesions

Response and efficacy of oncology agents has traditionally been measured by Response Evaluation Criteria in Solid Tumors (RECIST), a set of published rules that define when tumors respond, stabilize, or progress during treatment. However, due to the kinetics of the anti-tumor response associated with immuno-oncology agents, these criteria do not easily apply. Unlike conventional cytotoxic therapies that may trigger rapid tumor shrinkage due to direct killing of cancer cells, immuno-oncology drugs stimulate immune cell responses that may take several months to occur. In fact, patients may exhibit an initial increase in tumor burden followed by tumor shrinkage, a phenomenon called the flare effect.

Only applying RECIST criteria to immunotherapy trials can result in the following:

- Premature termination of therapy
- Unnecessary removal of patients from clinical trials
- Inaccurate interpretations of treatment response

In 2017, a new set of immune-related response criteria was proposed by a RECIST working group composed of members of industry, academia, the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA). This consensus guideline — called Immune RECIST (iRECIST) — is intended to help sponsors make decisions regarding continuation of therapy in clinical trials.

iRECIST calls for the use of modified RECIST in cancer immunotherapy trials and describes a standardized approach to measuring solid tumors and defining objective change in tumor size for clinical trials.[2] iRECIST also introduces a new response criterion known as immune unconfirmed progression of disease (iUPD), which describes new overall response.

With iRECIST, the bar for progression resets if RECIST-defined progressive disease (PD) is followed at the next time point (TP) by tumor shrinkage, as seen in TP2 in the figure below.

iRECIST has not yet been validated and should not be used as a guideline for treatment decisions. However, iRECIST may be used as primary response criteria in exploratory, early phase studies and can be used in conjunction with RECIST in later-phase studies. Sponsors who wish to use iRECIST guidelines in their studies should train their operational team and communicate closely with the Data and Safety Monitoring Board (DSMB) to ensure

that all stakeholders understand that immunotherapy agents work differently than cytotoxic therapies.

VALIDATING BIOMARKERS

While the immunotherapies that have been approved to date are effective for a subset of patients, many patients do not respond. Current response rates and toxicities associated with immunotherapies — along with their high cost — have created a sense of urgency to elucidate which patients would most benefit from these agents. Thus, there is pressing need for biomarkers to predict response to therapies.

The identification of immune-specific biomarkers will help to fill knowledge gaps by providing valuable predictive and prognostic information, as well as insights on the underlying mechanisms of treatment response and resistance. Potential sources of biomarkers include target protein expression, serum soluble proteins, circulating tumor cells, circulating cell-free DNA, and tumor gene expression.

To date, the techniques for examining biomarkers for immunotherapy include immunohistochemistry, in situ hybridization, flow cytometry, immunoassays, and next-generation sequencing, each of which has its pros and cons. New opportunities for biomarkers include the following:

- HLA typing
- Microbiome analysis for determining risk of inflammatory complications
- Tumor mutation burden (TMB) measured via whole genome sequencing, whole exome sequencing or comprehensive gene panel testing can be used to identify patients who have an increased response to immunotherapy
- T cell receptor repertoire clonality, which is associated with response to PD-1 inhibition and is currently being evaluated in clinical trials

Combining biomarker approaches may be a powerful way to both characterize the tumor and monitor the immune response, but requires close collaboration between technical and clinical experts.

Another major hurdle to the identification and development of clinically relevant biomarkers is the fact that immune modulation affects many cell types and involves complex interactions among the host, cancer cells, and tumor microenvironment.[3] The Society for Immunotherapy of Cancer (SITC) Biomarkers Task Force has published a series of white papers on the validation process and regulatory considerations associated with biomarkers in immunotherapy, as well as novel technologies and emerging biomarkers relevant to individualized cancer therapy.

FINDING THE RIGHT COMBINATION

Cancer treatment is undergoing a radical transformation in which conventional cancer treatments are being integrated with immunotherapeutic agents. Many clinical trials are evaluating the potential to further enhance the clinical benefits of monotherapies by combining agents with synergistic mechanisms of action. Combination therapies may combine the following:

- Agents that act at the effector stage (eg, anti-PD-1 or inhibitors of immunosuppression) by re-energizing pre-existing T cells
- Agents that act at the proliferation/activation stage (eg, anti-CTLA-4) to not only enhance pre-existing responses, but also stimulate de novo responses
- Agents that act on other co-stimulatory or inhibitory pathways

However, it has been shown that substantive incremental toxicity can result from these combinations, depending on the patient population, dose, and schedule utilized. For example, a Phase I study combining ipilimumab with vemurafenib, a Raf inhibitor, in patients with melanoma showed significant increases in toxicity at standard dosing. Further, active combination regimens may have distinct safety profiles in different populations, as illustrated by differences in tolerability to a combination of ipilimumab and nivolumab between patients with melanoma and patients with metastatic non-small cell lung cancer.[4]

In order to address the challenges of selecting rational combination therapies, the SITC convened a Combination Immunotherapy Task Force. This Task Force was charged with identifying and prioritizing the most promising candidates for combinatorial approaches, as well as tackling the challenges associated with developing these strategies. An overview of the current evidence supports the promise of using inhibitors of the PD-1 pathway as a backbone in combination therapies due their established anti-tumor activity and favorable toxicity profile.[4]

To maximize the likelihood of success, combination therapies require not only rig-

orous clinical testing early in clinical development, but also the willingness to accept the use of non-standard doses or schedules of individual agents to maximize the overall risk-benefit profile.

IDENTIFYING ADVERSE EVENTS

Especially with the shift toward combination immunotherapy, it is becoming increasingly important for sponsors and investigators to be adept recognizing, characterizing, and monitoring immune-related adverse events (irAEs) and other serious adverse events (SAEs).

In general, immunotherapy agents demonstrate unique safety profiles that may differ considerably from most conventional oncology drugs. For example, up to 23% of patients treated with ipilimumab develop SAEs, including colitis and hypophysitis.[3] When given in conjunction with dacarbazine, approximately 20% showed significant elevations of liver function tests.

Sponsors should keep in mind that toxicity does not accurately predict positive therapeutic outcome, and patients may experience irAEs or SAEs without benefiting from an anti-tumor effect. Training trial site staff, as well as patients, caregivers, and all members of the healthcare team, how to anticipate, recognize, and intervene on irAEs and SAEs will contribute to clinical trial success.

It is also important to remember that the appearance of irAEs may vary, and understanding the kinetics of these events is important for site training, patient management, and data monitoring. Consequently, protocols of immuno-oncology drug trials should clearly outline how immune-related toxicities should be managed. In addition, if new safety signals are identified, sponsors may need to prepare for rapid redesign of protocols and databases.

LOOKING TO THE FUTURE

Advances in our understanding of the immune response to cancer — along with recent advances in biomarker development — are increasing the number of patients with cancer who benefit from immunotherapy. As we look to the future, new immuno-oncology agents and combination approaches have the potential to further expand the spectrum of patients who respond to cancer immunotherapy, improving the quality of clinical responses and paving the way for a personalized approach to cancer treatment. ◆

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BIOGRAPHY

Luke S. Gill is Executive Director, Oncology, Strategic Development for Premier Research and has an extensive scientific background and more than 20 years of drug development experience. Specializing in oncology, he has led numerous global CRO management teams and provided strategic assessment, management, and oversight of study enrollment and program metrics. Prior to joining Premier Research in 2015, Mr. Gill was Director of Global Project Management for Hematology and Oncology at PPD, overseeing design and delivery of clinical development plans across multiple indications and specializing in early phase oncology. He also served as Assistant Project Management Director at PPD, was CRO Alliance Program Director for Merck Serono, and has held positions at Pfizer/Parke Davis, Astra, and Glaxo. Mr. Gill earned his MSc in Neuro and Molecular Pharmacology from the University of Bristol, his BS in Biological Sciences from the University of the West of England, and his MBA specializing in Strategy and International Enterprise from the Open University in the UK.

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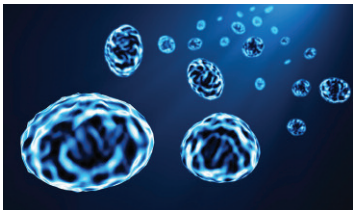

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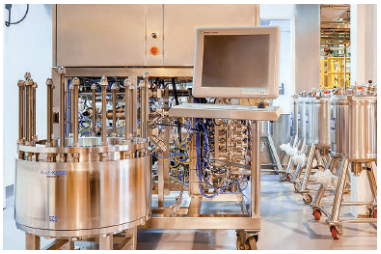

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