Drug Development & Delivery

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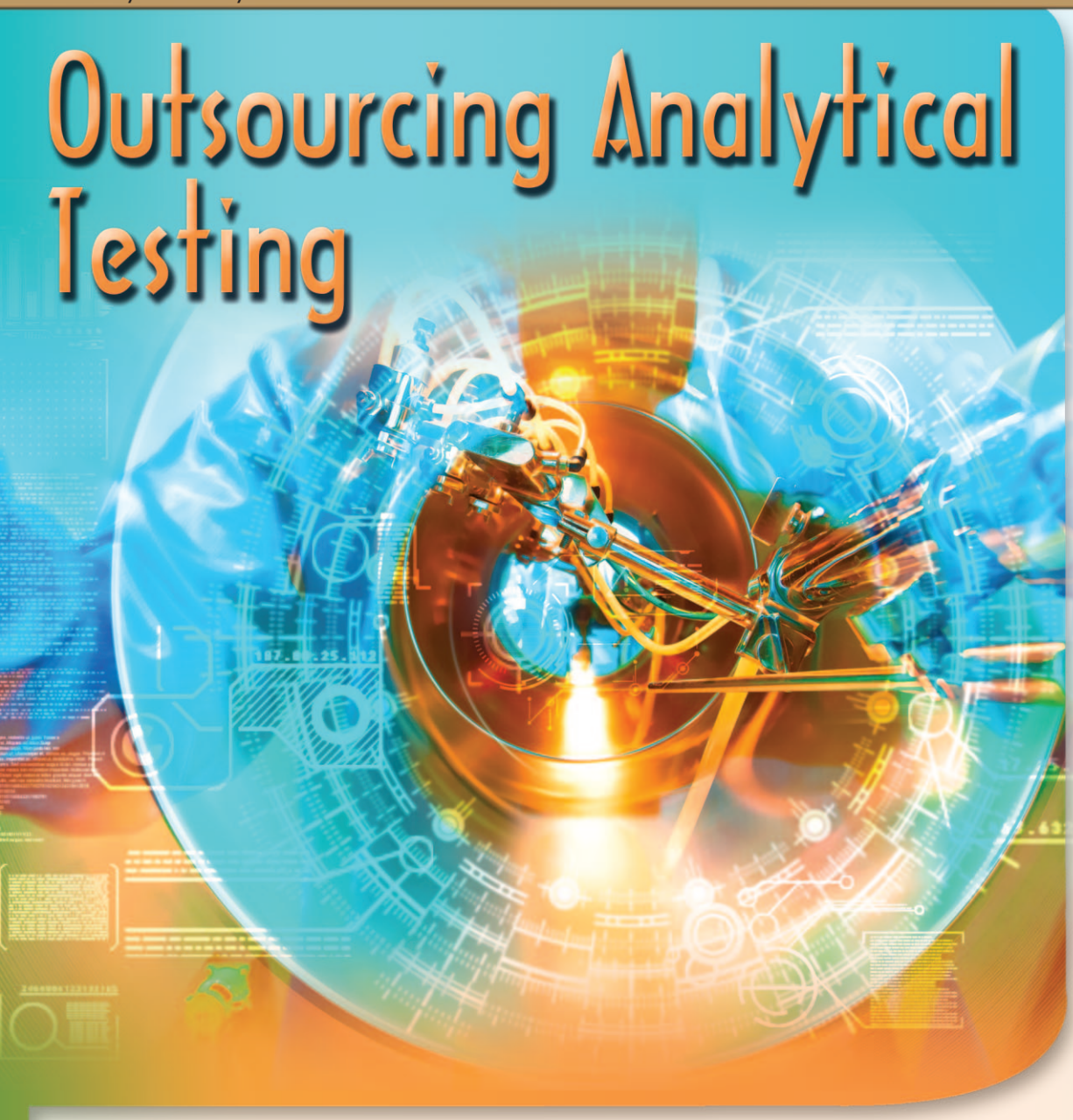
Outsourcing Analytical Testing



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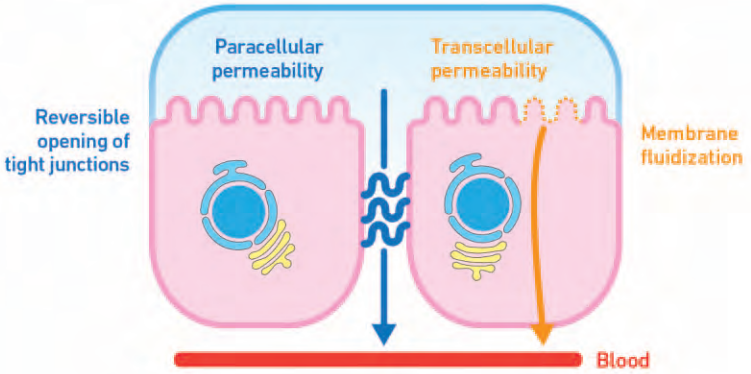

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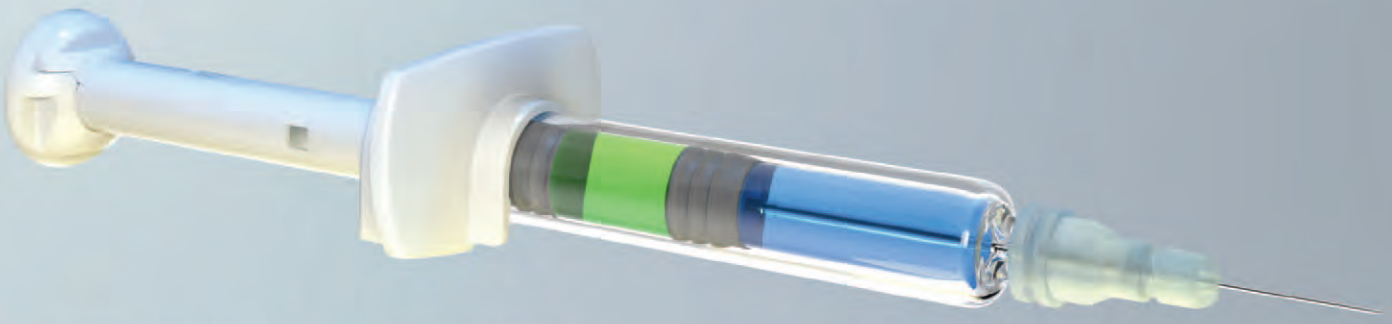

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Outsourcing Analytical Testing

"During the Covid19 pandemic, many pharmaceutical development projects were delayed or postponed due to lack of available resources within analytical labs, as well as the lack of ability to execute clinical studies due to quarantine restrictions. This has had a lasting impact on the industry as the desire to catch up to delayed timelines has driven the demand for more rapid and efficient analytical testing."

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A TECHNOLOGY-DRIVEN CDMO DELIVERING END-TO-END PATIENT-CENTRIC SOLUTIONS

TRANSFORMING DRUG DELIVERY. TRANSFORMING LIVES.

Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with small molecule expertise focusing on oral dosage forms. Adare's specialized technology platforms provide taste masking, controlled release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare has developed and manufactures more than 45 products sold by customers worldwide.

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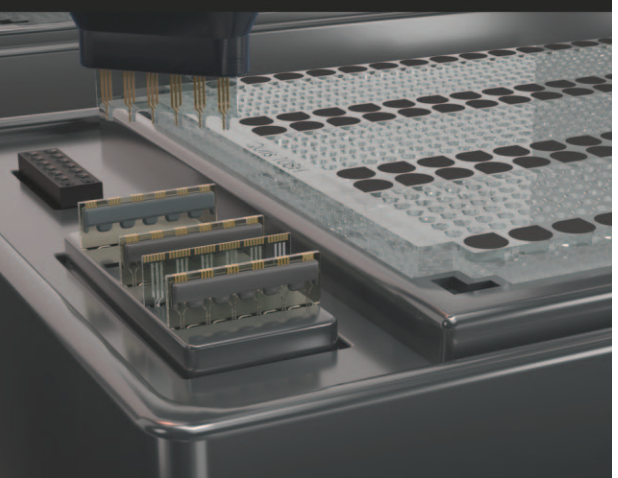
p.66



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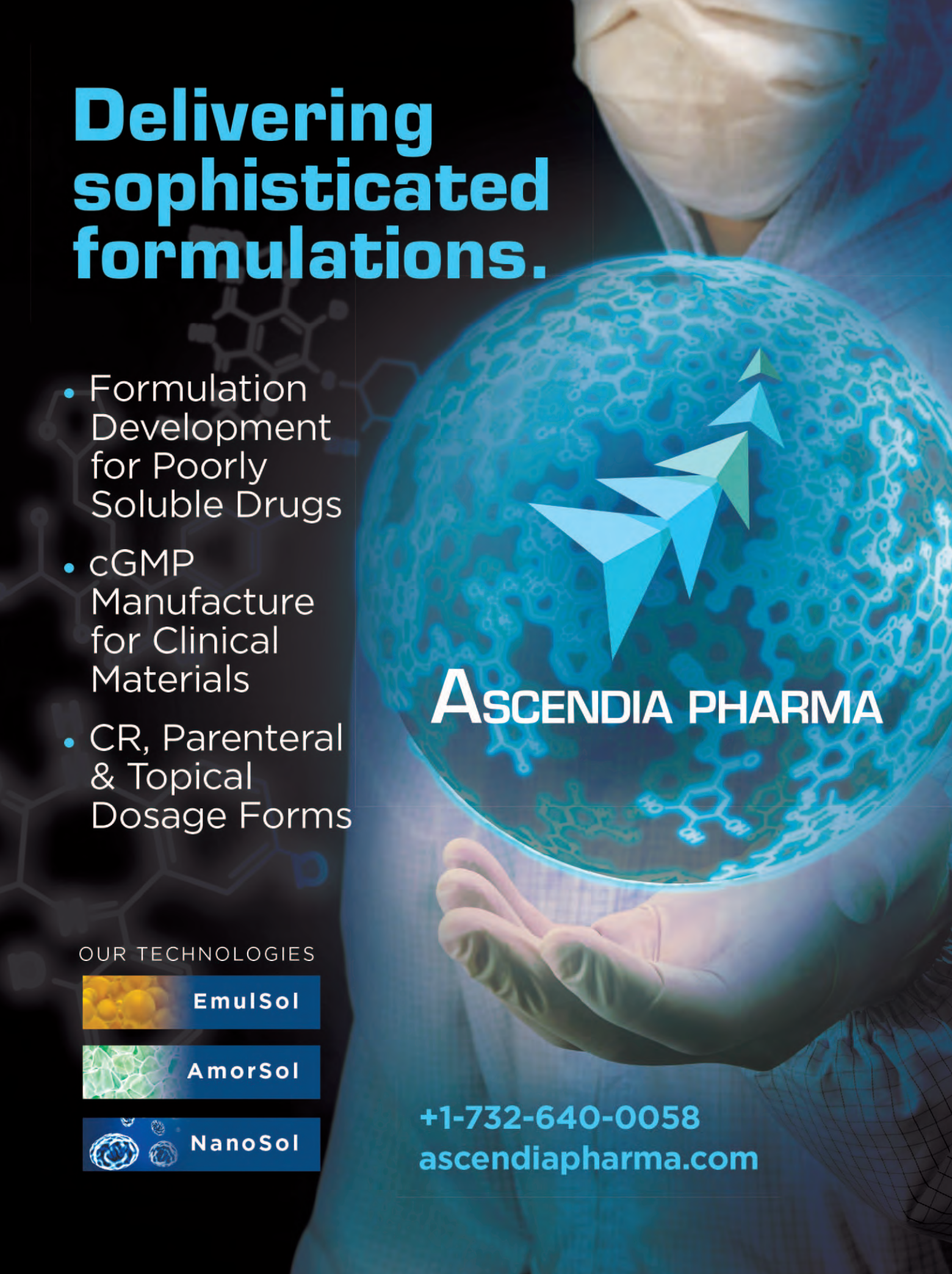
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Sterling Pharma Solutions Completes Acquisition of API Manufacturing Facility in Ireland

Sterling Pharma Solutions recently announced the completion of its acquisition of an active pharmaceutical ingredient (API) manufacturing facility in Ringaskiddy, Ireland, from Novartis, in a deal that was initially announced in March 2022. The facility will provide additional capacity for Sterling's growing API manufacturing services, and the deal includes an on-going supply agreement with Novartis to continue to manufacture a number of APIs for cardiovascular, immunology, and oncology medicines at Ringaskiddy. No financial details of the deal have been disclosed.

The 111-acre site, located near to Cork, includes multiple commercial-scale production buildings, with a total vessel capacity of 175 cubic metres across over 30 reactor trains, as well as a small-scale facility, and a development and support building housing 14 development and analytical laboratories. 350 staff at the site have now transferred to Sterling's employment.

Equipped to undertake a wide range of chemical reactions, including the handling of highly potent APIs, down to an Occupational Exposure Level (OEL) of 200 ng/cubic metre, technologies also include large-scale chromatography columns, solid phase and agitated vessels for peptide coupling and synthesis, as well as various milling and micronisation equipment for drug substance processing. Sterling plans to invest in the Ringaskiddy facility to grow its contract development and manufacturing pipeline, bringing additional jobs to the site over the coming years.

"The Ringaskiddy site has clear synergies with Sterling's other manufacturing facilities, and we have spent the last nine months working closely with staff to ensure a smooth integration into our global network to provide small molecule API development and manufacturing services for customers across the world in a range of therapeutic areas," said Kevin Cook, Sterling's Chief Executive Officer. "Strategically, the acquisition adds a European hub to our network, and not only expands our total capacity and workforce of highly skilled experts, but adds new capabilities in peptide manufacturing and large-scale chromatography."

The acquisition is part of Sterling's on-going business strategy, which has seen the company grow from a business in 2020 with 300 employees across two sites, to 1,300 employees based across five facilities in the UK, US and Europe.

Sterling Pharma Solutions is a global contract development and manufacturing organisation (CDMO) with more than 50 years of experience in providing small molecule API development and manufacturing services to the pharmaceutical industry, specialising in handling challenging chemistries. Sterling manages the most complex API challenges from proof-of-concept to commercial manufacture, as well as antibody-drug conjugate (ADC) research and development bioconjugation services. Sterling has five facilities employing more than 1,300 people: its HQ in Dudley, Northumberland, UK; the new site in Ringaskiddy, Co. Cork, Ireland; a dedicated bioconjugation and ADCs facility in Deeside, North Wales, UK; and two sites in the US, in Cary, NC, and Germantown, WI.

SAB Biotherapeutics Successfully Concludes IND-Enabling GLP Toxicology Study for Novel Immunotherapeutic for Type 1 Diabetes

SAB Biotherapeutics recently announced the successful completion of an IND-enabling GLP-tox study for SAB-142, further progressing the therapeutic as a way to prevent and/or delay onset and progression of type 1 diabetes (T1D) and potentially other T-cell mediated autoimmune diseases. The study assessed the toxicity and pharmacodynamic effects of SAB-142 against an FDA-approved T-cell depleting therapeutic at varying doses and found it to be well tolerated and showed a desired dose-dependent pharmacologic effect. SAB will submit the IND filing within approximately 12 months.

SAB-142 is the first fully-human anti-thymocyte hpAB therapeutic currently being developed for delaying the progression and onset of type 1 diabetes, among other autoimmune indications. Commercially available products for T-cell mediated autoimmune diseases, such as fully-animal antibodies and other monoclonal lymphodepletion therapeutics, require re-dosing and often induce immune-mediated reactions such as serum sickness. As a fully-human polyclonal antibody therapeutic, SAB-142 may be administered multiple times without causing these immune-related adverse reactions, a desired factor when treating life-long diseases such as type 1 diabetes.

"The completion of this GLP-tox study is an early, but significant milestone in the development of SAB-142 that enables a successful IND submission," said Alexandra Kropotova, MD, Chief Medical Officer of SAB. "We are eager to continue progressing this therapeutic, which we believe has the potential to impact the lives of millions of patients with varying autoimmune diseases, including those with type 1 diabetes."

In the study, SAB-142 was dosed at 1, 5, and 10 mg/kg and commercially available anti-thymocyte globulin was dosed at 5 mg/kg. The study results showed that both SAB-142 and its active control, FDA-approved animal-derived polyclonal anti-thymocyte immunoglobulin, induced transient lymphodepletion confirming the SAB-142 mechanism of action. The dynamics of the depletion appeared to be more prolonged in the cohort with SAB-142 treatment, which could create the opportunity for an optimized dosing regimen.

SAB Biotherapeutics, Inc. (SAB) is a clinical-stage biopharmaceutical company focused on the development of powerful and proprietary immunotherapeutic polyclonal human antibodies to treat and prevent infectious diseases and immune and autoimmune disorders. Our development programs include infectious diseases resulting from outbreaks and pandemics, as well as immunological, gastroenterological, and respiratory diseases that have significant mortality and health impacts on immune compromised patients. SAB has applied advanced genetic engineering and antibody science to develop Transchromosomic (Tc) Bovine. Our versatile DiversitAb platform is applicable to a wide range of serious unmet needs in human diseases. It produces natural, specifically targeted, high-potency, fully-human polyclonal immunotherapies without the need for human donors. SAB currently has multiple drug development programs underway and collaborations with the US government and global pharmaceutical companies.

Atavistik Bio Announces Collaboration With Plex Research to Enrich the Informatics Capabilities of its AMPS Platform & Accelerate the Discovery of Novel Small Molecule Therapeutics

Atavistik Bio recently announced it has entered into a collaboration agreement with Plex Research, a company providing a novel artificial intelligence (AI)-powered drug discovery platform. Atavistik Bio's incorporation of Plex Research's technology will enrich the informatics capabilities of its Atavistik Metabolite Protein Screening (AMPS) platform and accelerate its drug discovery pipeline.

Atavistik Bio's scalable AMPS platform combines an extensive and continually expanding protein-metabolite database map (the Interactome), along with advanced informatics tools, deep expertise in chemistry, and computationally rich structure-based design to systematically identify and understand the role of protein-metabolite interactions across important biological and disease-relevant pathways to inform small molecule drug discovery.

Under the collaboration, Atavistik Bio will enhance its proprietary Interactome map with Plex Research's cloud-based AI-powered drug discovery search engine of large and disparate data sources to reveal hidden connections between related metabolites and ligands, pathways, biomarkers, and disease-relevant biology. The integration of Atavistik Bio's AMPS data with Plex Research's platform will create a unique and customizable data analysis engine to rapidly enable novel insights for drug discovery.

"Allosteric interactions, which we know can present novel druggable nodes for intractable targets, historically have been difficult to discover. Using our AMPS platform, we are able to systematically and rapidly interrogate protein-metabolite interactions to reveal new, disease-relevant allosteric binding sites," said Marion Dorsch, PhD, Atavistik Bio's President and Chief Scientific Officer. "Fusing the enterprise-level capability of Plex's access to large public databases with Atavistik's proprietary data infrastructure has the potential to significantly augment the power of our AMPS platform and accelerate our efforts to drive the discovery of novel therapeutics for unmet patient needs."

"Atavistik's platform creates opportunities to drug proteins in new ways by uncovering previously unknown regulatory sites with potentially important roles in disease," added Doug Selinger, President and CEO of Plex Research. "The breadth and depth of the Plex platform will provide important context for Atavistik's AMPS data, which will enable better characterization of putative protein regulatory sites, ligand binding, and potential impacts on disease processes. The synergies between our technology platforms are compelling, and we're excited to see where it will take us."

Atavistik Bio is a biotechnology company that is harnessing the power of protein-metabolite interactions to add a new lens to drug discovery with the aim of transforming the lives of patients. By leveraging its optimized Atavistik Metabolite Protein Screening (AMPS) platform and computational approaches, Atavistik Bio aims to evaluate metabolite-protein interactions by screening proteins with their proprietary metabolite library to reveal where binding sites with biological function might exist.

Plex Research has developed a novel form of artificial intelligence (AI) based on search engine algorithms which can derive new insights from massive amounts of diverse biomedical data.

Vaccinex Announces First Patient Dosed with Anti-CCR8 Antibody Licensed to Surface Oncology

Vaccinex, Inc. recently announced its licensee, Surface Oncology dosed the first patient in its Phase 1/2 clinical study investigating SRF114, an antibody discovered using Vaccinex's ActivMAb antibody discovery platform and licensed to Surface Oncology in 2021.

"We are very pleased that Surface has progressed SRF114 into a Phase 1/2 clinical study. Advancing this promising drug candidate into the clinic provides positive validation of our proprietary ActivMAb antibody discovery platform," said Ernest Smith, PhD, Chief Scientific Officer of Vaccinex. "ActivMAb is particularly focused on antibody targets like CCR8, a complex GPCR protein. We are gratified that we were able to provide Surface Oncology with a potential best-in-class anti-CCR8 antibody and look forward to continued progress for the SRF114 program."

SRF114 is a potential best-in-class, fully human monoclonal antibody targeting, CCR8. SRF114 was designed to selectively deplete immuno-suppressive tumor T regulatory cells (Tregs) while sparing peripheral Tregs. The highly specific binding properties of the antibody are believed to position SRF114 as a potential best-in-class anti-CCR8 antibody as a monotherapy for the treatment of advanced solid tumors. Under the terms of the antibody discovery agreement, Vaccinex has the potential to receive progress-related clinical milestone payments and royalties on sales.

Vaccinex has developed a proprietary mammalian cell-based antibody discovery platform with unique multi-pass membrane target capabilities. The ActivMAb technology now has four main applications: complex membrane antigen presentation, antibody or antigen discovery, and protein optimization. Vaccinex has an antibody license agreement with Surface Oncology (Cambridge, MA) and the company is engaged in multiple other biopharmaceutical collaborations employing this enabling technology for drug discovery.

Vaccinex, Inc. is pioneering a differentiated approach to treating cancer and slowly progressive neurodegenerative diseases through the inhibition of semaphorin 4D (SEMA4D). The Company's lead drug candidate, pepinemab, blocks SEMA4D, a potent biological effector that it believes prevents immune infiltration into tumors and triggers inflammation in chronic diseases of the brain. Pepinemab is being evaluated in combination with KEYTRUDA in a Phase 1b/2 study in recurrent or metastatic head and neck cancer (R/M HNSCC) and as a monotherapy in a Phase 1/2a study in Alzheimer's Disease, with ongoing exploration of potential Phase 3 development in Huntington's disease. The company has also developed a proprietary drug discovery platform, ActivMAb, that it is leveraging thru strategic collaborations, particularly by applying its unique capability to select high value antibodies against important multi-pass membrane receptors.

Derm-Biome Pharmaceuticals' Multi-Target Topical Drug Produces Positive Results in Preclinical Study in Acne

Derm-Biome Pharmaceuticals, Inc. recently announced that in a preclinical trial run by the Dr. George Lui lab at the University of California San Diego (UCSD) School of Medicine, one of its topical lead compounds produced significant inhibitory effects in an animal model of acne, a common chronic inflammatory skin disease for which there is a significant unmet need.

Dr. George Liu, MD, PhD, and Professor and Chief of Pediatric Infectious Diseases at the University of California, San Diego, said "The results were quite promising for how effective the topical application reduced the disease score and the colony forming units. The disease score was particularly impressive. Based on our data, this product clearly outperforms benzoyl peroxide, a common anti-acne medication."

Acne is the most common chronic inflammatory skin disorder, with a prevalence of almost 95 percent in adolescents. The psychological impact of acne is substantial, causing profound negative social effects on the quality of life. There are currently no satisfactory treatments for acne that combine high efficacy and acceptable safety. The global acne treatment market size is forecast to reach as high as $16.9 billion by 2030 (Precedence Research).

Dr. Youwen Zhou, Derm-Biome co-CSO and Professor of Dermatology at the University of British Columbia, and Director of Skin Research Program, Vancouver Coastal Health Research Institute, said "These are very interesting results. Given the huge market size, and that the currently available topical treatments have limited efficacy or side effects, a novel, effective, and well tolerated topical therapy would be of high demand."

Dr. Andy Sham, PhD, Derm-Biome Scientific Advisor and project manager for the Gut4Health Microbiome Core at BC Children's Hospital Research Institute, added "The results from this trial are very promising. The compound appears to be very effective in limiting the disease by lowering the bacteria that can cause acne on the skin."

Derm-Biome CEO Gordon Eberwein, said "We continue to be impressed by the strong results from this non-steroidal topical drug. We feel that it has significant potential to be a first-line treatment for acne and atopic dermatitis, two inflammatory skin diseases with substantial unmet need."

Derm-Biome Pharmaceuticals, Inc. is a preclinical biopharmaceutical company dedicated to improving skin health. We have topical lead compounds for inflammatory skin diseases (acne and atopic dermatitis) and skin cancer that are both highly effective and well tolerated by skin. We are currently advancing our skin disease drug toward a Phase 1 clinical trial.

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Ajinomoto & Exelixis Enter License Agreement to Discover & Develop Novel Antibody-Drug Conjugates for the Treatment of Cancer

Ajinomoto Co., Inc. recently announced a license agreement with Exelixis, Inc. to incorporate AJICAP, Ajinomoto Co.'s proprietary site-specific bioconjugation and linker technologies, in the development of certain of Exelixis' antibody-drug conjugate (ADC) programs.

Exelixis is a commercially successful, oncology-focused biotechnology company that strives to accelerate the discovery, development, and commercialization of new medicines for difficult-to-treat cancers. Utilizing its network of biotherapeutics collaborations, the company is developing next-generation ADCs for the treatment of various cancers. Ajinomoto Co. is a leading technology provider for biopharmaceuticals and the owner of CDMO Ajinomoto Bio-Pharma Services. AJICAP is Ajinomoto Co.'s proprietary site-specific bioconjugation and stable linker technologies compatible with commonly used antibody isotypes. AJICAP technology includes its "off-the-shelf" feature, allowing any therapeutic antibody at any stage of development to be conjugated to drug-payloads of choice without the need for antibody engineering or cell line development, and stable/hydrophilic linkers to generate ADCs with an enhanced therapeutic window.

As part of the license agreement, Exelixis will have the right to use the AJICAP technology to support its aim of advancing multiple ADCs with the potential for higher efficacy and lower toxicity than currently available options. Ajinomoto Co. is eligible to receive development, regulatory, and commercial milestone payments as well as royalties on commercial sales.

Dr. Tatsuya Okuzumi, General Manager, Business Development Group, Bio-Pharma Services Department, Ajinomoto Co., said "We are very excited to support Exelixis, a leader in oncology drug discovery, development, and commercialization, in the development of novel ADCs. The combination of Exelixis' antibodies and payloads with Ajinomoto Co.'s AJICAP opens up a wide range of oncology applications and may be harnessed to provide a clinical benefit to patients."

Based on the corporate message Eat Well, Live Well., Ajinomoto Co., Inc. has been scientifically pursuing the possibilities of amino acids to aim for future growth by creating new value through sustainable and innovative solutions for communities and society. For more information, visit www.ajinomoto.com.

As its pharmaceutical arm, Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization (CDMO) with sites in Belgium, US, Japan, and India, providing comprehensive development, cGMP manufacturing, and aseptic fill finish services for small and large molecule APIs and intermediates. For more information, visit www.AjiBio-Pharma.com.

In addition, Ajinomoto Co. and Ajinomoto Bio-Pharma Services offer a broad range of innovative platform technologies and capabilities for pre-clinical and pilot programs to commercial quantities, including AJIPHASE oligonucleotide manufacturing technology, CORYNEX and TALAMAX protein expression systems, AJICAP site-specific conjugation and linker technologies for ADCs, continuous flow manufacturing and more. For more information, visit https://ajibio-pharma.ajinomoto.com/.

Absci First to Create & Validate De Novo Antibodies With Zero-Shot Generative AI

Absci Corporation recently announced the ability to create and validate de novo antibodies in silico (via a computer) with the use of zero-shot generative AI — a major milestone for the biotechnology industry. The ability to create de novo therapeutic antibodies in silico could potentially reduce the time it takes to get new drug leads into the clinic from as much as 6 years down to just 18-24 months while also increasing their probability of success in the clinic. This new advancement is a major industry step change, unlocking the potential to deliver breakthrough therapeutics at the click of a button, for every patient.

Historically, biologic drug discovery is risky, time-consuming, and expensive, with a >90% failure rate. It takes an average of 10 years and >$1 billion to bring just one new drug to market, limiting the scope and number of treatments that drugmakers can pursue.

Absci used zero-shot generative AI — a method that involves designing antibodies to bind to specific targets without using any training data of antibodies known to bind those specific targets. Absci's model produced antibody designs that were unlike those found in existing antibody databases, and the zero-shot designs worked in the lab right out of the computer — without the slow and costly step of further optimizing the in silico designs in the lab.

Absci's breakthrough demonstrates generative AI as an alternative to traditional biologic drug discovery, potentially unlocking treatments for traditionally "undruggable" diseases and improving therapeutic possibilities for many others.

Scalable biological data has been one of the biggest barriers to applying generative AI to biologic drug discovery. Absci overcomes this challenge with its proprietary high-throughput wet lab technology, which today is capable of testing and validating nearly 3 million unique AI-generated designs each week — well above the industry standards. This wet lab data is an invaluable component for improving generative AI models and creating better antibody designs. Absci can accomplish this design to data cycle in a timeframe of weeks.

Absci further demonstrated its wet lab's ability to experimentally validate the superiority of de novo antibody candidates to bind to the target antigen — all without lead optimization of the in silico designs — in cycle times as little as six weeks. Absci validated antibodies for HER2 and multiple additional targets.

The achievement is also the first example of a generative AI engine designing new therapeutic antibodies by designing the heavy chain complementarity determining region 3 (HCDR3) from scratch, where the computational design has been wet-lab validated to bind to the intended targets. HCDR3 is a critical region for antibodies to bind to their targets and enable their therapeutic potential.

DropControl minimizes the spontaneous dropping of ophthalmic preparations

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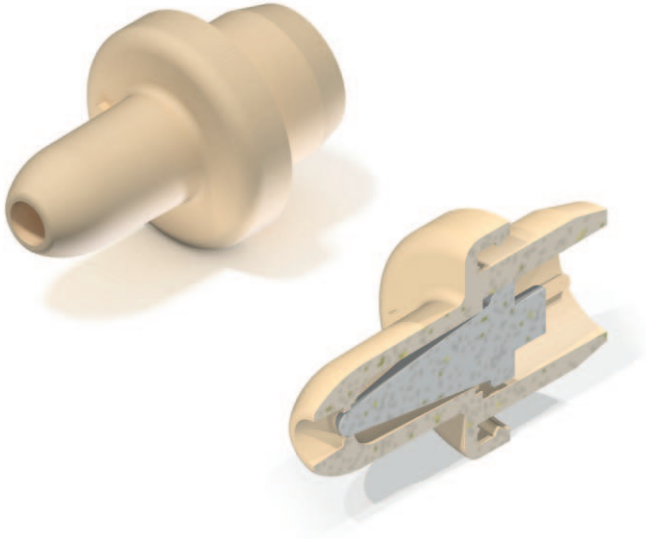

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Celltrion & Rani Therapeutics Partner on Development of Oral Monoclonal Antibody Treatment

Rani Therapeutics Holdings, Inc. recently announced it has partnered with Celltrion for the development of RT-111, an orally administered ustekinumab biosimilar.

Under a license and supply agreement, Celltrion will exclusively supply to Rani the ustekinumab biosimilar drug substance (CT-P43) required for RT-111. Rani is granted an exclusive license to use CT-P43 in the development and commercialization of RT-111, and Celltrion is granted a right of first negotiation to acquire worldwide rights to RT-111 following a Phase 1 clinical trial.

Rani has developed an oral delivery technology known as the RaniPill capsule, which is intended to replace subcutaneous or intravenous injection of biologics and drugs with oral dosing. The RaniPill capsule is designed to administer biologics and drugs with bioavailability comparable to subcutaneous injection.

"We are delighted to be partnering with Celltrion, a leader in biosimilars and biologics manufacturing, on RT-111. This agreement is a validation of our RaniPill oral drug delivery technology, which has already performed well in two separate Phase 1 trials of RT-101 and RT-102, respectively," said Talat Imran, CEO of Rani. "We value Celltrion as the exclusive provider of ustekinumab biosimilar for our RT-111 program and look forward to sharing the results of our study in due course, and potentially broadening our partnership with Celltrion."

"Celltrion strives to address unmet needs of patients and partnering with Rani offers the opportunity to replace painful injections with a pill," said SungHyun Kim, Head of Medical Science Division. "Celltrion sees potential for the RaniPill platform to be applicable to other biologics."

Rani Therapeutics is a clinical-stage biotherapeutics company focused on advancing technologies to enable the development of orally administered biologics and drugs. Rani has developed the RaniPill capsules, which are a novel, proprietary and patented platform technology, intended to replace subcutaneous injection or intravenous infusion of biologics and drugs with oral dosing. Rani has successfully conducted several preclinical and clinical studies to evaluate safety, tolerability, and bioavailability using RaniPill capsules. For more information, visit ranitherapeutics.com.

IMUNON Enters Collaborative Research Agreement With The Wistar Institute's Vaccine & Immunotherapy Center to Research IMUNON's PLACCINE Vaccine Platform

IMUNON, Inc. and The Wistar Institute recently announced the signing of a first collaborative research agreement to research and develop new vaccine formulations utilizing IMUNON's PLACCINE modality for the development of vaccines for infectious diseases. IMUNON's platform technologies are based on the delivery of nucleic acids with novel synthetic delivery systems.

"We are delighted to enter into this collaborative research agreement with The Wistar Institute Vaccine & Immunotherapy Center, possessing world renowned expertise in cancer, immunology, infectious diseases, and vaccine creation. Wistar is uniquely positioned to advance new vaccine formulations in collaboration with IMUNON," said Dr. Corinne Le Goff, President and Chief Executive Officer of IMUNON. "This collaboration will facilitate further expansion and development of PLACCINE with the goal of expanding vaccine targets ideally matched for our novel formulated DNA delivery platform and further optimizing quality attributes and the immunity of products."

IMUNON is a fully integrated, clinical-stage biotechnology company focused on advancing a portfolio of innovative treatments that harness the body's natural mechanisms to generate safe, effective and durable responses across a broad array of human diseases, constituting a differentiating approach from conventional therapies.

IMUNON has two platform technologies: the TheraPlas modality for the development of immunotherapies and other anticancer nucleic acid-based therapies, and the PLACCINE modality for the development of nucleic acid vaccines for infectious diseases and cancer. The company's lead clinical program, GEN-1, is a DNA-based immunotherapy for the localized treatment of advanced ovarian cancer currently in Phase II development. GEN-1 works by instructing the body to produce safe and durable levels of powerful cancer-fighting molecules, such as interleukin-12 and interferon gamma, at the tumor site. Additionally, the company is conducting preclinical proof-of-concept studies on a nucleic acid vaccine candidate targeting the SARS-CoV-2 virus to validate its PLACCINE platform. IMUNON's platform technologies are based on the delivery of nucleic acids with novel synthetic delivery systems that are independent of viral vectors or devices. IMUNON will continue to leverage these platforms and to advance the technological frontier of nucleic acid-based products to better serve patients with difficult-to-treat conditions. For more information, visit www.imunon.com.

The Wistar Institute, the first independent, nonprofit, private biomedical research institution in the US, marshals the talents of an international team of outstanding scientists through a highly enabled culture of biomedical collaboration and innovation to solve some of the world's most challenging and important problems in the field of cancer, immunology and infectious diseases, and produce groundbreaking advances in world health. The Wistar Institute's history of researching and supporting development of new vaccines and biologics against targets of global importance including Rabies, Rubella, Rotavirus, Cell lines for Live Attenuated vaccines, polio vaccine strains, New Adenoviral vaccines, Nucleic Acid based vaccines as well as for generating of biologics makes them a strong partner.

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Sterile & Non-Sterile Formulation Capabilities - A CDMO Perspective

By: Jim Huang, PhD, Founder & CEO, and Shaukat Ali, PhD, Sr. Director, Scientific Affairs & Technical Marketing, Ascendia Pharmaceuticals Inc.

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Shauket Ali, PhD
shaukat.ali@ascendiapharma.com

INTRODUCTION

With continued rise in new innovative molecules with poor water solubility and low bioavailability, the industry's landscape in developing these molecules has been brought to a new height. Finding the right technologies for bringing in and developing these molecules is one aspect, whereas identifying the appropriate manufacturing processes capable of handling and packaging the sterile products is the other. The latter brings challenges and raises the phenomenal risks.[1] To alleviate all these hurdles and to optimize the complexity, especially in sterile manufacturing of parenteral drugs, small molecules, large molecules, or gene therapies, the industry is looking for partnership with contract manufacturing organizations (CMOs) to avoid any unexpected delays, circumvent the cost, and expedite the manufacturing and commercialization of innovative and complex generic molecules without compromising safety of drug products.[2]

Ascendia, like any other CDMO, is expanding its footprints in sterile manufacturing to handle the innovative molecules and leverage its services to emerging and specialty and biopharma companies requiring cGMP materials for preclinical tox and clinical studies. Its expertise in cGMP manufacturing of oral liquids, capsules and tablets, and sterile injectable dosages for clinical and commercialization are at the par.[3]

As shown in Table 1, Ascendia maintains options for sterilization with lyophilization capability for liquid and powder fills under aseptic conditions of a pilot facility with more than 5,000 units per batch with 100 sq ft, while a medium-to-large facility with 1,500-sq-ft and 10,000-sq-ft capacities can fill 24,000 units and 150,000 units per batches, respectively. All these suites meet the ISO classification 5. On the other hand, the non-sterile facilities also meet ISO classifications 7 and 8 and are able to handle 100,000 units per batch and more than 100,000 units per batch within the processing area of 4,000 sq ft and 15,000 sq ft, respectively. Our state-of-the-art aseptic filler can handle different vial sizes for various drug products, yielding greater flexibility to our clients.

TABLE 1

Capability	Sterile Dosage Form			Non-Sterile Dosage Form	
	Pilot sterile	S-1 sterile	S2-large sterile	Early Phase 1/2	2-Commercial
Capacity	5 suites with freeze dryer (Pre-fill syringe/Vial)	4 suites (Pre-fill syringe/Vial)	5 suites (Vial)	5 suites	8 suites
ISO Classification	100/10,000	10/10,000	100/10,000	100,000	100,000
Output	5,000 units per batch	24,000 units per batch	150,000 units per batch	100,000 units per batch	> 100, 000 units per batch
Processing Area	100 sq ft	1,500 sq ft	10,000 sq ft	4,000 sq ft	15,000 sq ft

Ascendia's capacity and capabilities in sterile and non-sterile manufacturing

TABLES 2A & 2B

Sterilization Method	Condition	Pros	Cons
Dry Heat	180°C for 30 min or 170°C for 1 hour or 160°C for 2 hours	Kills pyrogens	API/excipient heat sensitivity matters
Autoclave/Moist Heat	121°C for 15 min	Requires certain heat/moist temperature	API/excipient heat/moisture dependent instability
Sterile Filtration	0.2-micron filter	Filter integrity checked/maintained	Applicable to temperature/heat sensitive lipids/nanoparticles and similar assemblies
Gamma/E Beam Irradiation	25-kGy effective	Containers and packaging materials stable	Not recommended for heat sensitive APIs/excipients

Table 2A. Sterilization methods and the challenges

Process	Challenges	Pros	Cons
Lyophilization	Compatibility of drugs with sugars and excipients used as cryoprotectants	Long term stability and facilitates re-constitution in solution	Time consuming long process, expensive
Cyclodextrin	Associated with kidney toxicity	Ease of formulation, stability and complexing ability with aromatic compounds	Cavity size interferes with complexation
Surfactants	Majority polyethoxylated fatty acids, side effects with castor oil-based surfactants	High solubilization abilities, lipophilic micellize drugs	Higher amount could be toxic and can cause damage to tissues
Liposomes & LNPs	Stability, encapsulation	Natural and synthetic lipids, versatile preparation, higher drug loading with LNP	Long-term stability and non-specific in targeting cells

Table 2B. Modalities to improve solubility of drug in parenteral formulations

GENERAL SCOPE OF STERILIZATION

Terminal sterilization is accomplished by a number of procedures to ensure the safety and quality of drug products are maintained over extended shelf-life. Table 2A and Table 2B show the methods and challenges for sterilization of drug products and modalities for improving solubility of parenteral drug products, respectively.[4]

Parenteral product's sterility is an important attribute for product safety. Therefore, the FDA regulations on the current good manufacturing practice (cGMP) must be followed to avoid the delays and fines, and most importantly, maintaining the safety of drug products.[5] For drug products intended for sterilization, a specific method is chosen considering the stability of drugs and other ingredients in the products. Table 2A gives the choices for selecting one method over others. Aseptic processing is eventually used for many of the sterile parenteral formulations to avoid contamination with humans or cross contamination with other products in the proximity.

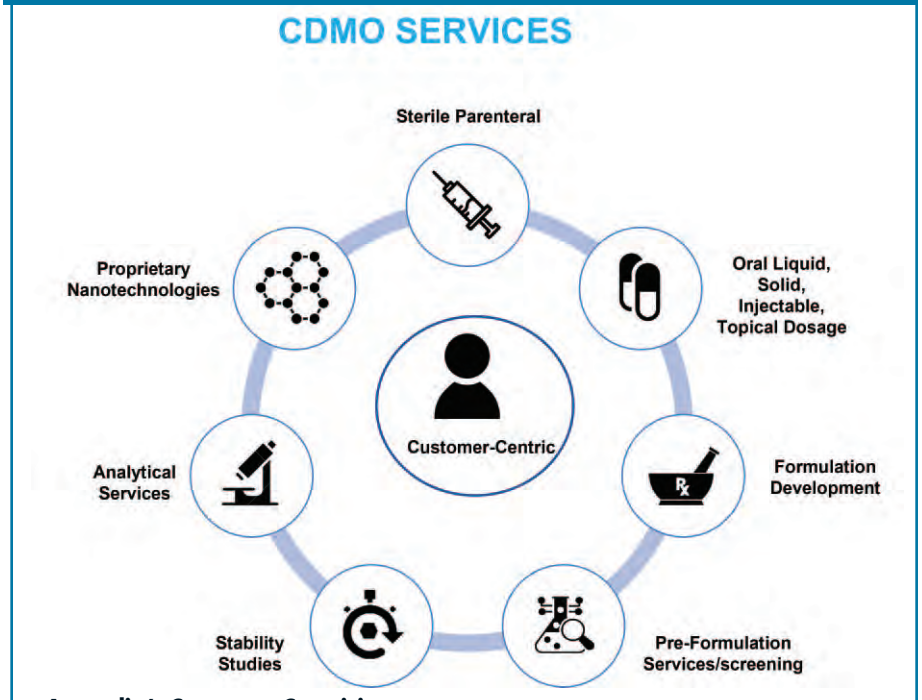
In addition to cGMP manufacturing sterile capabilities, Ascendia offers a range of R&D services to support the quality from early screening and pre-formulation to formulation design and manufacturing of clinical supplies. Figure 1 shows Ascendia's customer centricity by offering services to its clients in formulation and drug development of small and large molecules for different modalities requiring innovative approaches like NanoSol®, EmulSol®, LipidSol®, and AmorSol® platform technologies. Ascendia's expertise and capabilities in analytical testing and method validation under ICH guidelines enables clients to work with sterile injectable and non-sterile oral products for life saving aliments.

SUMMARY

As the pharma and biotech industry continues to innovate complex molecules, especially, large molecules, RNA/DNA, and biologics, the demand for CDMOs specializing in sterile manufacturing of parenteral formulations will grow with leaps and bounds. The FDA continues to push for cleaner and

isolated rooms for sterile products to minimize human errors due to cross contamination during aseptic fill processing. These changes can often introduce additional risks to the sterile fill/finish process, resulting in production delays, additional costs, and safety concerns. Parenteral formulations, for instance, developed as lyophilized dry powders, liquid suspensions, long-acting injectables, nanoemulsions, microemulsions, liposomes, or LNPs may require special equipment and dedicated sterile facilities for characterization, manufacturing, and release testing of drug products. Notably for such formulations, quality of water for injections for IV administrations need to be checked routinely for pH variations and/or any undesired contaminants, including bioburdens and pyrogens/endotoxins to ensure the stability of drug products over extended shelf-life. The stability of these formulations is critical as the impurities formed over shelf-life either caused by hydrolysis or oxidative degradation, heavy metals, racemization, or isomerization could lead to risk for batch failure due to compromised potency of drugs. That means CDMOs like Ascendia Pharma with the capabilities in handling the sensitive molecules will stay ahead of the curves and will be ready to tackle these challenges requiring formulation and bioanalytical support. ◆

FIGURE 1



Ascendia's Customer Centricity

FIGURE 2

Lipid Nanoparticles Processed by Microfluidizer

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DRUG-ELUTING IMPLANTS

Sustained-Release Implants - A Targeted Approach to Drug Delivery

By: Tom Quinci, MSc

INTRODUCTION

While the pandemic created a catalog of challenges for the pharmaceutical industry, it created opportunities and learnings too – most notably in terms of the speed with which companies can transform new, innovative approaches, like mRNA vaccines, into market-ready products. The success of the COVID vaccine roll-out saved countless lives and raised the bar on what an acceptable time to market is. This demonstrates the levels of accomplishment that can be realized when industry, regulatory agencies and governments are sufficiently motivated. Building on this momentum, we have an opportunity to carry that game-changing mentality forward and apply it to other challenges.

Such positive, expansive thinking can deliver improved drug modalities, overcome long-standing therapeutic hurdles, and develop approaches that mitigate the historic challenges of targeted delivery, dose accuracy, and patient adherence.

THE OPPORTUNITY TO DEPLOY NEW LEARNINGS FOR ONCOLOGY TREATMENT

According to estimates from the World Health Organization (WHO) in 2019, cancer ranks as the first or second leading cause of death before the age of 70 years in 112 of 183 countries and ranks third or fourth in a further 23 countries.[1]

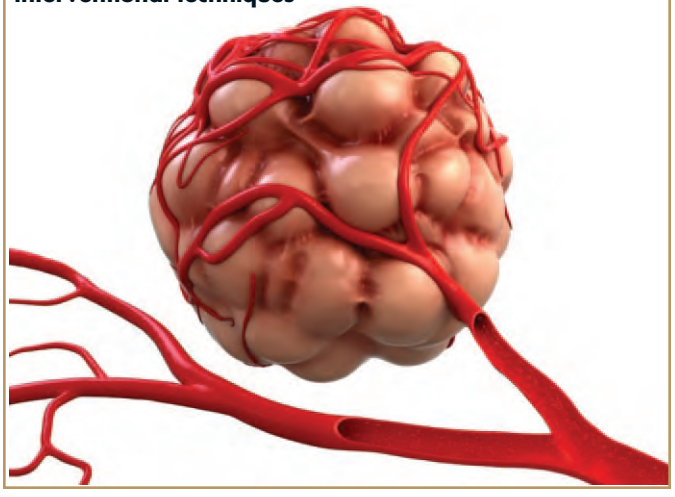
Cancer is a generalized name under which a multitude of diseases, each requiring a different therapeutic mode of action, are categorized. In terms of treatment options and patient outcomes, traditional routes of administration like oral, intravenous, and subcutaneous administration present their own risks and opportunities. In addition, patient acceptance, treatment burden, and the financial impact must also be considered. As new therapeutics are considered, we hope to move towards options that render obsolete the statement, "the treatment is worse than the disease." As such, we propose exploring a new approach to treatment of some solid tumor cancers (Figure 1).

SUSTAINED-RELEASE IMPLANTS BASED ON GAME-CHANGING DRUG DELIVERY TECHNOLOGY

Used extensively for years in the delivery of contraceptive therapies, biodurable implantable drug delivery systems have a decades-long clinical history. However, there is still uncertainty in

FIGURE 1

Solid tumors, a vascularized and heterogeneous mass of tissue, are directly accessible through a variety of interventional techniques



some quarters about the idea of implants for other types of therapies. Fueled by degrees of emotional response and supposition, there is a misconception they are too invasive to administer and after depleting their drug load, they need to be removed. The added safety and reliability benefits a biodurable implant may offer can be considerable, and the more implants are understood by practitioners, the more these benefits can be realized. It's important to note that every type of cancer is different and requires unique solutions.

In a Celanese-commissioned research study conducted with medical and surgical oncologists, more than 80% expressed that an implant-based therapy would be attractive or very attractive based on improved efficacy and reduced toxicity. The clinicians surveyed cited a number of benefits expected to most significantly reduce the treatment burden for patients, including reducing the frequency of office visits, reducing drug administration times, reducing the frequency of dosing, and minimizing the "poking and prodding."[2]

There is quite a bit of evidence to suggest implants should be considered (Table 1) and investigated more thoroughly and earlier in the drug product development process. Their ability to deliver drugs more effectively to a targeted treatment site, while addressing dose-limiting (systemic) toxicities, has the potential to overcome the inherent limitations faced with conventional forms of drug delivery – especially in effective targeting, lower toxicity. and patient adherence (Figure 2).

DRUG-ELUTING IMPLANTS CAN BRING NEW LIFE TO ESTABLISHED MEDICINES

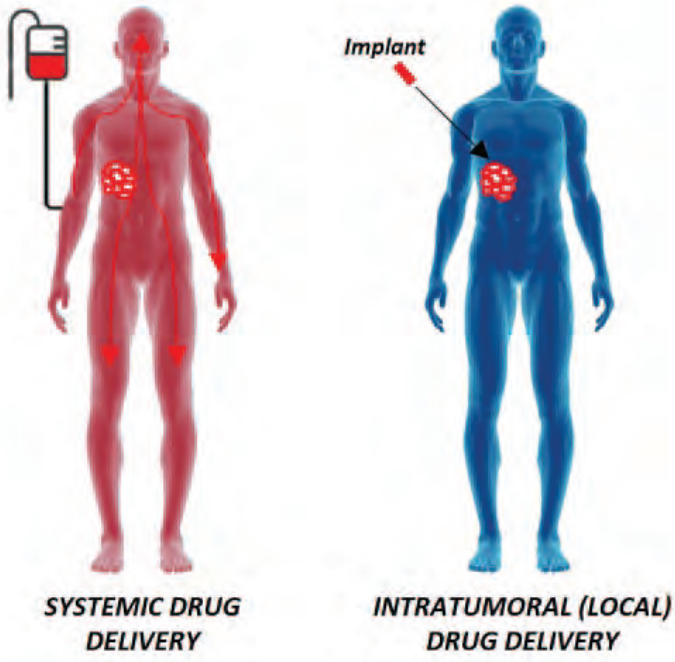
Drug repurposing refers to reformulating an existing, marketed drug product by finding new routes of administration, indications, or therapy areas. We all recognize that the commercialization of new drug therapies requires at least ten years of development work and can represent around a $2.6 billion investment.[4] Lever-

TABLE 1

Product Name	Implant Type	Material	Drug Delivered	Indication
Zoladex®	Sub-cutaneous	PLGA	Goserelin	Prostate cancer
Prostap®SR	Sub-cutaneous	PLGA	Leuprolide	Prostate cancer
Gliadel Wafers®	Intra-tumoral	Silicone	Carmustine (BCNU)	Primary malignant glioma
Oncogel®	Intra-tumoral	PLGA-PEG-PLGA	Paclitaxel	Oesophageal cancer
Vantas®	Sub-cutaneous	Methacrylate based hydrogel	Histrelin	Prostate Cancer

Examples of implantable drug delivery devices used for anticancer therapy.[3]

FIGURE 2



A drug-eluting intratumoral implant delivers therapeutics directly to targeted anatomic sites, potentially reducing off-target effects and systemic toxicity

aging safety data from an existing drug and reformulating for new routes of administration, indications, and therapy areas (lifecycle management) is a key area of focus as pharmaceutical partners seek to continue building intellectual property.

There are several potential economic benefits to repurposing an existing drug for implantable drug delivery, including reduced development costs, intellectual property to extend the patent-protected life of a drug, increased market share, and an extended life cycle. Implantable devices can also resolve a currently unmet medical need. Patient empowerment increases with reduced reliance on medical staff intervention and supervision, enabling them to exercise greater agency and control of their lives. Most importantly, there is an opportunity to improve patients' quality of life by potentially reducing the number of interventions, overall treatment burden, and the length and frequency of clinic visits.

IMPROVEMENTS IN TARGETING & BIOAVAILABILITY

It's no secret most drugs do not reach the market. According to the National Institutes of Health (NIH), 80% to 90% of research projects fail before they ever get tested in humans.[5] Some challenges that may result in the formulation being abandoned include poor solubility, limited bioavailability, high toxicity, and the inability to achieve sufficient drug concentration where needed. Poor absorption, distribution, metabolism, and excretion (ADME) properties are also among the factors that contribute to the failure of a drug to meet its market potential.

The proximity of an implant to the targeted region can increase the bioavailability of a molecule. As a result of localized implant delivery, lower drug volumes are needed to elicit the desired therapeutic effect. By optimizing the device to meet the needs of each drug, there is an opportunity to ensure the greatest clinical benefit for the patient. Simply put, implantable devices deliver the right drug, in the right place, at the right time.

FIGURE 3

Reducing the time and frequency of treatments could significantly improve quality of life and well-being for the patient

Implantable drug delivery systems also present formulators with an opportunity to improve success rates by reducing the likelihood of off-target effects, which may improve patient tolerance.[6-8] By implanting the device close to the site of action, there is an opportunity to reduce systemic exposure and mitigate the damage caused to healthy cells.

A CRITICAL BALANCE BETWEEN EFFICACY & TOXICITY

Healthcare providers (HCPs) are often faced with a precarious balancing act, working to maintain treatment while mitigating the adverse effects of what are very often highly toxic drugs. Many chemotherapies and immunomodulators have major to minor toxicities. For example, pulmonary toxicities include interstitial pulmonary fibrosis (IPF), usual interstitial pneumonitis (UIP), pneumonitis, radiation recall-pneumonitis, and alveolar hemorrhage.[9]

Consequently, when presented with toxicity effects, HCPs will pull back on treatment frequency or dosage and, in some cases, end the treatment regime. This is clearly a far from optimal outcome for patients, and one that may be avoided with a more targeted, sustained-release delivery mechanism.

CARING FOR THE HUMAN, NOT JUST THE PATIENT: A GAME-CHANGING OPPORTUNITY

Cancer and the therapies it demands impact patients' lives in all kinds of ways. Everyday life is limited or otherwise impacted due to fatigue, nausea, or pain, and there is the burden of numerous and time-consuming visits to clinical settings. Implantable devices offer several patient-

centric benefits to overall well-being and improved mental health, as well as relief from some of the physical cost, time, and stress of repeated hospital or clinic visits (Figure 3).

AN OPPORTUNITY TO REIMAGINE DRUG DELIVERY, A CHANCE TO BE BRAVE

If the pandemic has shown us anything, it is that important innovations can be brought to market quickly, when propelled by the right resources, collaborations, and commitment. Oncology requires new treatment modalities that are better for patients, and it is time technologies like drug-eluting implants are more widely considered. Implantable sustained-release drug delivery devices offer real, achievable advantages: sustained continuous dosing, potential to improve drug-delivery efficiency by concentrating the drug where it is needed most (while minimizing systemic exposure and any resulting side effects), and built-in adherence.◆

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BIOGRAPHY

Tom Quinci has a diverse background in the development of therapeutic delivery systems, including drug products and interventional medical devices. At Celanese, he is responsible for developing strategic commercial partnerships and technical collaborations, while also leading ideation and concept development for applications in oncology, ophthalmology, and central nervous system disorders. Prior to Celanese, he held positions at DSM Biomedical and W.L. Gore and Associates, where he led key programs for orthopedics and electrophysiology. He earned his Bachelor's degree in Mechanical Engineering and a Master's degree in Engineering Management. He completed post-graduate programs through the Oklahoma Heart Institute and Wharton School of Business.

Special Roundtable

Which Trends Will Have the Most Impact on Drug Development in 2023?

By: Cindy H. Dubin, Contributor

Drug Development & Delivery posed this question to life science leaders during a recent roundtable discussion. One common theme is the focus on sustainability in pharmaceutical development. This ranges from reducing carbon footprints to decreasing solvents in formulations. Another area of agreement among roundtable participants in that oral solid drugs (OSDs) will continue to dominate the drug delivery market. But some are taking a unique approach to OSD development with 3D technology. And speaking of technology, some life science leaders point to "Pharma 4.0," where technology will be used to accelerate and streamline drug development.

DR. MICHAEL QUIRMBACH
President & CEO,
CordenPharma

"ESG is Key"

Sustainability is a topic of increasing importance for all in the pharmaceutical industry, including CordenPharma, going forward in 2023. We keep these values at the core of what we do. At the top of our agenda is Environmental, Social and Governance (ESG). We started working a couple of years ago with companies such as Ecovadis, and our new shareholder Astorg – a private equity company with a big emphasis on ESG – so of course they are expecting that level from the companies in their portfolio. We are working to get all our facilities approved at the highest level of Ecovadis sustainability rating (gold). Also, what we see today is that our customers, particularly the larger pharma companies, are putting a lot of emphasis on ESG, so they look for that in a supplier. They want to make sure we are using the right processes to reduce our carbon footprint and increase health and safety standards. It's going to get much more attention than in the past. It's the right thing to do. Big Pharma companies need to not only set a target for themselves, but also choose suppliers that know how to implement ESG targets. It must be throughout the whole supply chain – that's key.

VINCENT JANNIN
Head of Capsule Applications Services,
Lonza CHI

"Unique Development for Oral Drug Products"

2022 has seen new and emerging technologies and advanced formulation and manufacturing techniques for targeted oral drug delivery. Breakthrough innovations in capsule materials and engineering are providing enteric protection for drugs that are heat- or acid-sensitive or cause gastric irritation. This is important as it prevents gastric acids in the stomach from dissolving or degrading drugs after they are swallowed. Lonza CHI has developed an empty capsule with built-in enteric release profile and acid protection that eliminates the need for enteric coating. This will minimize the amount of work needed during process development, scale-up, and validation programs. Demand for oral medication is expected to remain high as most patients prefer oral dosage forms due to their convenience and cost-effectiveness. Therefore, it is expected manufacturers will continue to focus on unique ways to develop and create drug products with advanced technologies. TiO2 is extensively used in oral solid dosage forms due to its multiple functionalities. In January 2022, the European Commission published Regulation (EU) 2022/63 banning the use of the food additive TiO2 (E171) in foods across the European Union as from August 7, 2022. The same legislation urges pharmaceutical companies to make any possible efforts to accelerate the research and development of alternatives for titanium dioxide in medicinal products and to submit the necessary variations to the terms of the marketing authorizations concerned. Lonza has developed innovative Capsugel® White hard gelatin capsules that can serve as a replacement for TiO2. As opposed to CaCO3-containing capsules, the Lonza alternative matches the whiteness, opacity, and performance obtained with the reference gelatine capsules containing TiO2. Next to white alternatives, a wide range of color formulations allowing to create a unique visual appearance is available. Our formulation specialists remain available to evaluate appropriate capsule options.

JOHN BAUMANN
Director of R&D, Head of Advanced Engineering Technologies,
Lonza Small Molecules

"Solubility Through Sustainability"

A trend that has been increasing for the past few years, but shows no sign of abating is the number of poorly soluble drugs in the clinical pipeline. One way that solubility – and therefore bioavailability – can be improved is through the creation of an amorphous solid dispersion, or ASD. But this is intertwined with another

trend: the desire to make processes more sustainable. ASDs are commonly made via spray drying. However, this requires large volumes of flammable or chlorinated solvents. To address this, Lonza has developed a temperature-shift spray drying process, where a pressurized slurry of the drug and dispersion polymer is heated rapidly, and then atomized into the drying chamber via a bespoke flash nozzle. The result is an ASD that is identical to one made at room temperature. The process is faster, reduces the volume of solvent, and uses more benign solvents, greatly improving its sustainability. Another alternative is to use hot-melt extrusion, where the drug is mixed with a dispersion polymer, heated up, and passed through an extruder. While it does not work for all drugs – the drug must be thermally stable and have adequate miscibility or solubility at the process temperature – it is cheaper than spray drying. But, importantly, no solvents are involved, which makes for an inherently safer and more sustainable process. With the growing call for sustainable manufacturing, we are sure to see even more technologies to reduce or eliminate solvent use to create drug formulations.

TOM WILSON
VP, Global Business Development Lead,
Pfizer CentreOne

"CDMOs Must Mold to Become True Partners"

In the coming year, CDMOs will need to be better equipped to react to the industry's needs in a dynamic landscape and help companies meet key milestones and the expectations of various stakeholders, including investors, and most importantly, patients. Agility and flexibility, not just in manufacturing capability and capacity, but in contract structures, and terms of payment to meet the sponsor's cash flow requirements. The perennial pressure on pharmaceutical companies is project timelines, which can be affected by the partnership with a CDMO. Streamlining workflows to better suit a company's needs is an effective way to keep timelines short and drug development efficient. Addressing these challenges will be vital in helping companies meet their development milestones. Within the biologics space, huge advancements being made with mRNA vaccines and cell and gene therapies are shifting regulatory approaches and pathways. These changes can be difficult for emerging biotech companies or other pharmaceutical companies to navigate or even understand as there is so much fluidity. This is an area where CDMOs can show their added value beyond being competent manufacturers. Partnering CDMOs will need to work more closely with their customers in the coming years to mold their working model to suit the company and its stakeholders. The more a CDMO can flex and adapt in the spirit of becoming a true partner, the greater its chances of forming successful, sustainable relationships that help ensure vital medicines can make it to patients.

JOHN MCDERMOTT
Vice President of Scientific Consulting,
Quotient Sciences

"Single-Service Platform Accelerates Development"

The pharmaceutical industry is constantly seeking ways to accelerate the drug development process and shorten timelines to reduce costs and deliver medicines to patients earlier – 'trends' which are followed annually in the industry. The margins between companies are very close, and accelerating drug development by finding ways to streamline processes is an important aspect of remaining competitive and relevant to healthcare and patients. One approach to accelerate drug development is to integrate drug substance, formulation development, clinical trial manufacturing and clinical testing into a single, common service platform. The integration of drug manufacturing and program strategy management works to streamline key stages of drug development and fast-track a molecule from first-in-human to proof-of-concept. Aspects of drug development that benefit from a single

common service platform include supply chain issues, downtime between trials, decision making, and knowledge retention. Streamlined processes and integrated operations can shorten development program timelines drastically and allow the next study to start that much sooner – and of course, there is a significant amount of money and effort attached to that time. Importantly, by initiating studies and analysis sooner, the lessons learned from them can be implemented faster, reducing the time and expense of obtaining clinical trial results. Ultimately, that is how pharma will ensure patients receive safe, effective medicines more efficiently and affordably.

DR. UWE HANENBERG
Head of Product Development, Oral Solid Dose,
Recipharm

"Biologics in the OSD Space"

The rise of oral biologics will be a major theme in the oral solid dose (OSD) segment in 2023. Traditionally, biologics are administered parenterally, despite the relative inconvenience to patients, due to the sensitivity of the active ingredients to degradation in the gastrointestinal tract. However, advances in OSD technology means that some biologics, such as insulin, can now be developed for oral delivery, allowing the biopharma space to take advantage of the unique patient convenience benefits of OSD. Nevertheless, drug developers face issues when formulating oral biologic treatments that they need to overcome. Support from OSD formulation experts will be crucial to biotechs in 2023 to address these barriers to development.

Another major trend impacting the OSD space is the growing demand for small-batch manufacturing to support the orphan drug market. Commercializing these therapies effectively poses a challenge for drug developers – by their nature, these diseases are rare, affecting a small number of people worldwide, meaning only small volumes of drug product are required. As such, new commercial paradigms and manufacturing processes are required to make them financially viable. 3D printing of OSD forms is one option that is increasingly being considered to manufacture small batches of these medicines cost-effectively. We can expect demand for contract manufacturing partners with 3D printing capability to grow through 2023 and beyond. Artificial intelligence will also impact drug development over the next 12 months, particularly within the OSD space. Machine learning, for example, can improve data analysis during discovery and development to maximize the chances of OSD project success.

JAMES CHOI
Executive Vice President, Chief Information and Marketing Officer,
Samsung Biologics

"Digitizing Drug Discovery & Delivery"

The pharmaceutical industry is increasingly adopting digital tools, such as data-driven drug discovery and integration of AI and machine learning, to improve drug development and navigate the manufacturing complexities of biological drugs. This digitalization is part of a broader industry transformation, "Pharma 4.0," where technology is being used to accelerate and streamline drug development. The digital transformation of biopharma holds promise to improve the efficiency of drug delivery to patients. The transformation, however, lacks cohesion and consistency despite great expense and effort. Many companies lag behind with old technologies, and the digital infrastructure of biopharma is compromised by outdated legacy systems, siloed approaches, and poor data integrity, which struggle to support the integration of digital technologies. Simplification should be at the heart of digitalization. Achieving this requires a robust strategic plan centered on optimizing operational or business processes. Rather than aiming to go paperless with a digital format, the goal should be to make the process easier and streamlined for the employee in the process of digitalization. Although the digital future of the pharmaceutical industry is still evolving, the path has become much more well-defined and tangible. The viable technologies are available now, but they must be well integrated into existing frameworks. Achieving effective digitalization requires a counterintuitive digitalization strategy, where the focus shouldn't be on finding the technological solution but on improving the existing manual process. A robust approach that identifies clear goals for digital transformations is how technologies can overcome the complexi-

ties of manufacturing biologics. This integration of data-driven drug discovery has great potential to benefit drug development pipelines and commercialization. The digital transformation of the pharmaceutical industry should also improve the lives of patients through the efficient delivery of therapeutics.

SARA LESINA, MBA
General Manager Business Unit Europe,
Sirio Europe

"Sophisticated Nutraceutical Science Supports Consumer-Centric Applications"

The therapeutic effectiveness and consumer appeal of nutraceuticals will increasingly be driven by pharmaceutical-grade science and applications. Nutraceuticals' role in healthcare is rising in prominence with research fueling tremendous innovation across the sector to increase the consumer appeal and therapeutic value of these products. Consumers are now taking nutraceuticals to help treat or manage a broad range of conditions, and industry analysts agree that the COVID-19 pandemic clearly accelerated consumer demand for nutraceutical products that contribute to better physical and mental health outcomes. The momentum of the market post-pandemic is undeniable with industry analysts projecting the global nutraceuticals market to grow from the approximately $350 billion it is today to approximately $650 billion by 2030.[1,2] Nutritional science is advancing its understanding of the chemistries and therapeutic potential of a myriad of different nutritional compounds and extracts. But it is important to remember the entire category is driven primarily by consumers, who are increasingly selective about the supplements they buy. Consumer preference for example is driving developers to innovate and introduce increasingly sophisticated formulations in popular formats like softgels and gummies. It is a completely free-market consumer choice and something that sets the industry distinctly apart from pharma. Consumers want their nutraceuticals to possess five essential things: taste and texture, health benefits, be free from additives, environmentally friendly, and non-GMO. They also want them to be easy to chew, swallow, and afford. To attain those mass-market product goals and meet consumer demands, the industry will be increasingly prompted to access more application science from its external pharmaceutical-grade manufacturing partners.

GERJAN KERMPERMAN
COO,
Ardena

"Nuanced CDMO Partnerships for Oncological Development"

Emerging biopharma companies own nearly 80% of oncology therapeutics in the early stages of the drug development pipeline and around two-thirds in the late stages. The growth of the oncology therapeutic sector is also shown in the research and development pipeline, where anti-cancer drugs outpace the overall pipeline growth. The rapid growth of oncology therapeutics is leading many biotechs to rely on partnerships with specialized CDMOs that have manufacturing and regulatory expertise. This shift to strategic partnership is a trend for 2023 that will see biotechs acquiring CDMO knowledge and facilities to aid drug development of novel oncology drug products in early phase development. The oncology therapeutic pipeline is comprehensive and the technologies in play are vast, therefore more diligence is needed when identifying and selecting a CDMO as industry needs are becoming increasingly nuanced. The manufacture of these compounds can be difficult, and many highly potent compounds require specialized facilities, equipment, and handling that are expensive to integrate within a biotech company. Notable advances have been made in the treatment of cancers from innovations in science and technology. These innovations also come from advances in manufacturing through purification and isolation that propel drug development forward. Examples include the development of sophisticated and large High-Performance Liquid Chromatography (HPLC) and advances in lyophilization units. CDMOs experienced in purification and isolation processes can ensure that biotechs give their product every chance to reach commercialization. ◆

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FUNCTIONAL EXCIPIENTS

Improving the Water Solubility of Oral Drugs With Amorphous Solid Dispersions (ASDs)

By: Liliana Miinea, PhD

INTRODUCTION

In 2020, more than 40% of new drug approvals in the US, Europe, and Japan were for oral administration and more than half of these were oral tablets.[1] Oral solid dosage forms are one of the most popular drug delivery methods due to the ease involved in self-administration, handling, and transportation.[2] These factors provide desired convenience to patients, thus patient compliance, when compared to some other routes of administration.

Despite the large number of drugs in development and the obvious advantages of oral dosage forms, the growth of this segment is hindered by the fact that nearly 90% of the drugs in the pipeline have poor solubility. The improvement of drug solubility and subsequent oral bioavailability remains one of most challenging aspects of the drug development process. One method that is becoming increasingly popular to address oral drug solubility issues is the use of amorphous solid dispersions (ASDs).

WHAT ARE ASDS?

An ASD is a solid dispersion in which the API is dispersed within an excipient matrix in a substantially amorphous form. Developments throughout the past few decades in synthetic polymers have enabled ASDs to emerge as an effective oral delivery strategy for overcoming poor drug solubility in aqueous environments. The polymer carrier stabilizes the drug in amorphous form, enabling long-term storage stability and improved dissolution when compared to the crystalline or pure amorphous drug forms.[4]

Drug-polymer ASDs can be prepared using hot-melt extrusion and spray-drying. In hot-melt extrusion, the drug and the polymer carrier are heated up to their melting point and mixed. Upon cooling of the melt, the drug is trapped within the carrier matrix in an amorphous state. In spray-drying, the drug, polymer carrier, and any other excipients are dissolved in a suitable solvent to form a liquid feedstock. In a continuous process, the liquid feedstock is sprayed into a heated air stream. Due to fast solvent

evaporation, the liquid feedstock droplets rapidly dry, entrapping the amorphous drug in the polymer matrix in the form of a solid powder.

WHAT ARE THE ADVANTAGES OF USING ASDS OVER OTHER DELIVERY METHODS?

There are many approaches to enhance the delivery of poorly water-soluble drugs intended for oral solid dosage. Many of these formulation strategies have distinct disadvantages. Lipid-based formulations can be associated with low drug loading, causing stability problems.[6,7] Solubilization in micelles is frequently associated with colloidal instability when introduced to bile salts in the stomach.6 Self-emulsifying drugs are often poorly tolerated in the long-term due to the surfactants used.[8] Micronized suspensions are often associated with slow and incomplete dissolution.[9]

ASDs provide an attractive alternative approach to these formulation methods. In a study examining 40 research papers, 82% of ASD formulations were found to increase or maintain bioavailability of a drug *in vivo*.[10] With the right polymer choice, many crystalline drugs can be stabilized in an amorphous form through ASDs. Depending on the drug-polymer system, a much higher drug load could be achieved using ASD delivery methods compared with other solubilization techniques. In addition, the development and manufacturing of ASDs rely on pharmaceutical processes that are well understood and easily scalable, including hot-melt extrusion and spray-drying.

ACHIEVING THE FULL POTENTIAL OF ASDS

Despite the advantages ASDs can provide for oral solid drug delivery, they account for only ~0.6% of drug products on the market today.[10] This suggests ASDs' potential has not been fully explored in today's drug development.

One challenge that must be overcome when developing and manufacturing ASDs is preventing recrystallization of APIs to increase their long-term stability.

Studies have shown that the addition of specialized polymers can help stabilize ASDs against crystalization.[12] Linear polyacrylic acid (PAA), for example, is a polymer that has been shown to both stabilize ASDs and increase the API solubility when prepared using solvent evaporation techniques, such as spray drying.[13-15]

An example of a speciality polymer currently available is the Apinovex™ polymer manufactured by LLS Health. This high molecular weight linear polyacrylic acid excipient can effectively enable physically stable, spray-dried ASDs, allowing for flexibility in drug loading of up to 80% API.

With such polymers, it is possible for drug formulators to take full advantage of the benefits of ASDs, enabling them to overcome formulation challenges to deliver more effective novel drug products capable of transforming the lives of patients. ◆

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BIOGRAPHY

Dr. Liliana Miinea is a Technology Manager with Lubrizol Life Science Health. Her work focuses on developing new technologies for pharmaceutical applications mainly in the area of controlled release, drug solubility enhancement, and enhanced mucosal delivery. She has more than 20 years of experience in developing and characterizing ingredients, including nanomaterials, polymer/nanomaterials composites, and novel excipients. Prior to Lubrizol she worked at Avantor Inc., NJ, and conducted post-doctoral research at Washington University in St. Louis, and Center for Nanomaterials Research at Dartmouth College, US. She earned her PhD in Chemistry from the University of Houston, TX.

CLINICAL TRIALS

Historical Controls in Rare Disease Drug Development: Using RWE to Overcome Key Challenges

By: William Maier, MD, PhD

INTRODUCTION

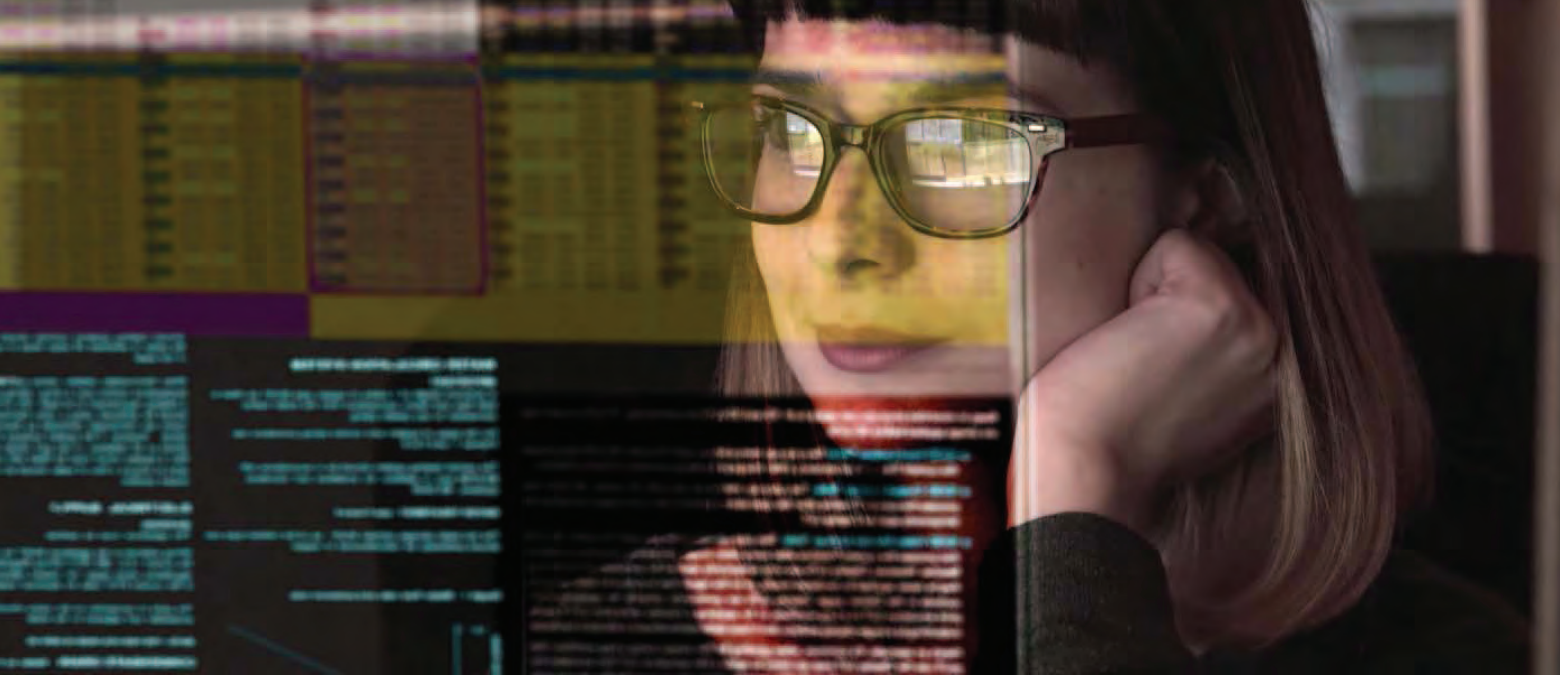
Rare disease drug development poses unique challenges that can be overcome by using real world evidence (RWE). Small populations, pediatric patients, and the desire from patients and their caregivers to receive active therapy can make the conduct of randomized trials with placebo control untenable.

As an alternative, regulatory agencies have allowed the use of RWE to estimate a historical control (HC) compared to patients enrolled in an uncontrolled study. Additionally, healthcare payers understand HCs can provide value by describing potential treatment benefit relative to untreated patients in their populations. The following will explore the advantages of using HCs, as well as several considerations for their effective use, including scientific methodology and regulatory guidance.

BENEFITS OF HISTORICAL CONTROLS

HCs can offer several advantages over concurrently collected control groups. For example, they can be created from multiple sources of disease natural history information. Disease natural history describes the demographic, genetic, environmental, and other variables (eg, treatment modalities, concomitant medications) that relate to the disease's development and outcomes over the course of disease. Natural history information also describes the current standard of care or emergent care, which may alter disease morbidity and mortality. Sources include ongoing prospective studies, such as patient registries, retrospective data from medical charts, control populations from previous trials, and expert opinion.

Another benefit is fewer patients are required in clinical trials using HCs, thereby reducing time to trial completion and speeding drug approval. However, the HC group needs to be very similar to the treated group in all respects, including outcome assessment, disease severity, duration of illness, prior treatments, and other aspects of the current standard of care that could affect the measurement and timing of treatment outcomes. To address



these limitations, researchers may use selection techniques that consider independent risk factors that may bias the assessment of the key treatment outcomes in order to match control subjects to the patients enrolled in the active treatment arm.

HC information has been successfully used to gain drug approval — for example, Brineura (cerliponase alfa) was approved to slow the loss of ability to walk or crawl in symptomatic pediatric patients three years of age and older with CLN2 disease.[1] Historical information on CLN2 patients was obtained from the DEM-CHILD database. As three domains of the rating scale used as primary outcome were measured differently between the database and the clinical study, the primary efficacy endpoint was limited to a single domain of this motor scale. The differences in the patient populations were addressed by matching controls to specific patient characteristics (specifically, baseline motor score, baseline age, genotype, gender, and age of first symptom) in the active treatment population. The FDA concluded the improvement in the active treatment group was not affected by the original differences identified between the active and HC population and approved the drug in April 2017.

SCIENTIFIC METHODOLOGY

Two different methodologies are used in the application of HC information in clinical development. The first, Bayesian statistical methodology, uses estimates from historical data to generate a prior probability distribution representing expected event rates for the outcome of interest in a trial. This is then combined with the observed data from the clinical trial to create an estimate, known as the posterior distribution, which is essentially a weighted average of the prior and the observed data from the clinical study. The application of Bayesian methodology has been recognized by the FDA as useful in early phase clinical trials involving pediatric populations.[2] Applications include more realistic estimates of adverse event rates in small populations; drawing statistical strength from adult data to make decisions about device performance in pediatrics; and shortening trials through use of adaptive designs and predictive probability of trial success before all patients finish the trial.

The second, frequentist methodology, involves the direct comparison of patient-level information from historical data to patients in the clinical study. This provides an approach using similar statistical methods to those used in a randomized clinical trial. The lack of randomization is likely to introduce bias due to differences between the historical and trial population. The differences may be reduced by several different strategies, including restriction of the patient population entering the HC; matching of the HC to increase similarity with patients in the active arm; and statistical methods to adjust for observed differences. Propensity scores, which are the probability of treatment assignment conditional on observed baseline characteristics, have been used to adjust for multiple patient factors in non-randomized studies.[3] The propensity score allows for the design and analysis of a non-randomized study so that two or more groups of patients with similar characteristics are compared in the assessment of treatment effect.

The decision to take a Bayesian or frequentist approach to using historical information is generally influenced by the availability of subject-level information to compare with the active trial arm and the

preference of regulatory agencies in a specific disease area or application. International regulatory agencies have normally favored direct comparison of patient-level data rather than estimated rate approaches when an HC is completely substituted for a concurrent control arm in a Phase 3 or registration study.

REGULATORY & PAYER GUIDANCE

Regulatory agencies in the US and Europe have been exploring the use of disease natural history information in drug development. Recently, the FDA published draft guidance outlining the different sources and applications of natural history information, including identification of patient populations, trial planning, and the use of HC information to establish drug safety and efficacy.[4] The EMA has also published their own guidance for the use of historical controls as part of its guidance on the conduct of trials for small populations.[5]

Healthcare payers also use clinical trial evidence to assess the effectiveness of treatments in making reimbursement decisions. These assessments often need to involve comparisons against multiple alternative therapies that would be impractical in the context of clinical drug development. The use of HCs can provide a comparative population not studied in the clinical trials. Some formal health technology assessment (HTA) guidance on the use of external controls and RWE is available from the UK's National Institute for Health and Care Excellence (NICE).[6,7]

A recent analysis of international HTA submissions from 2011-2019 found out of 433 submissions that involved the use of single arm trials, 52% contained some type of supplementary dataset that can be designated as HCs — most often from prior clinical trials, real world data, or both.[8] Submissions that contained external controls based on RWD had the most positive recommendations (59%) followed by submissions with prior trial ECs (49%). This suggests the widespread incorporation and acceptability of HCs in drug reimbursement decisions.

SUMMARY

RWE from rare diseases is available from a wide variety of sources for use as an HC in rare disease drug development. HCs are used in drug approvals, HTAs, and in describing the impact of new therapies in different clinical settings for rare diseases. As a result, the utility of HCs based on RWE should be evaluated for potential applications to increase speed of product approval, reimbursement, and clinical practice adoption. ◆

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BIOGRAPHIES

Dr. William C. Maier, MD, PhD, Vice President, Rare Disease, Drug Development Sciences at ICON. He has over 25 years of experience in drug development and commercialization at pharmaceutical companies in Europe, Canada, the US and Asia. At ICON he works with pharmaceutical companies throughout the world to provide regulatory, strategic, and scientific guidance on medical treatment development and commercialization. He is a member of the EMEA's European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (www.encepp.eu). In addition, he is a frequent speaker at medical conferences, has had academic appointments in the UK (Dundee) and the US (North Carolina) and is a member of the Royal Society of Medicine in the UK.

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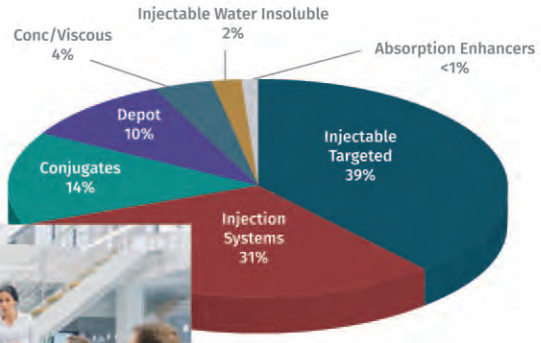

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DISCOVERY PLATFORM

Reverse-Engineering Targeted Immunotherapy

By: Bob Lechleider, MD

THE MODERN ERA OF CANCER IMMUNOTHERAPY

Cancer therapy has undergone a profound change over the recent past with the introduction of successful therapies that specifically target the human immune system. Cancer immunotherapy originally dates to 1891 with the observation that admixtures of two bacteria could cause regression in patients with sarcoma.[1] But it took about 100 years for the FDA to approve the first drugs specifically targeting the human immune system for the treatment of cancer with the approvals of interleukin-2 and interferon-alpha in the 1990s. These two cytokine products activate lymphoid and other cells in a fairly non-specific manner, and the high doses administered often lead to severe complications and require administration in specialized settings. The modern era of targeted immunotherapy was ushered in with the approval of the first T-cell checkpoint inhibitor (CPI), the anti-CTLA-4 agent ipilimumab, in 2011 for the treatment of metastatic melanoma. This was quickly followed by approvals for antagonists of PD-1 and PD-L1, the two key molecules important for regulation of T cells within the tumor. With these approvals, clinicians now had agents that targeted specific components of the immune system that could induce activated T cells to attack cancers.

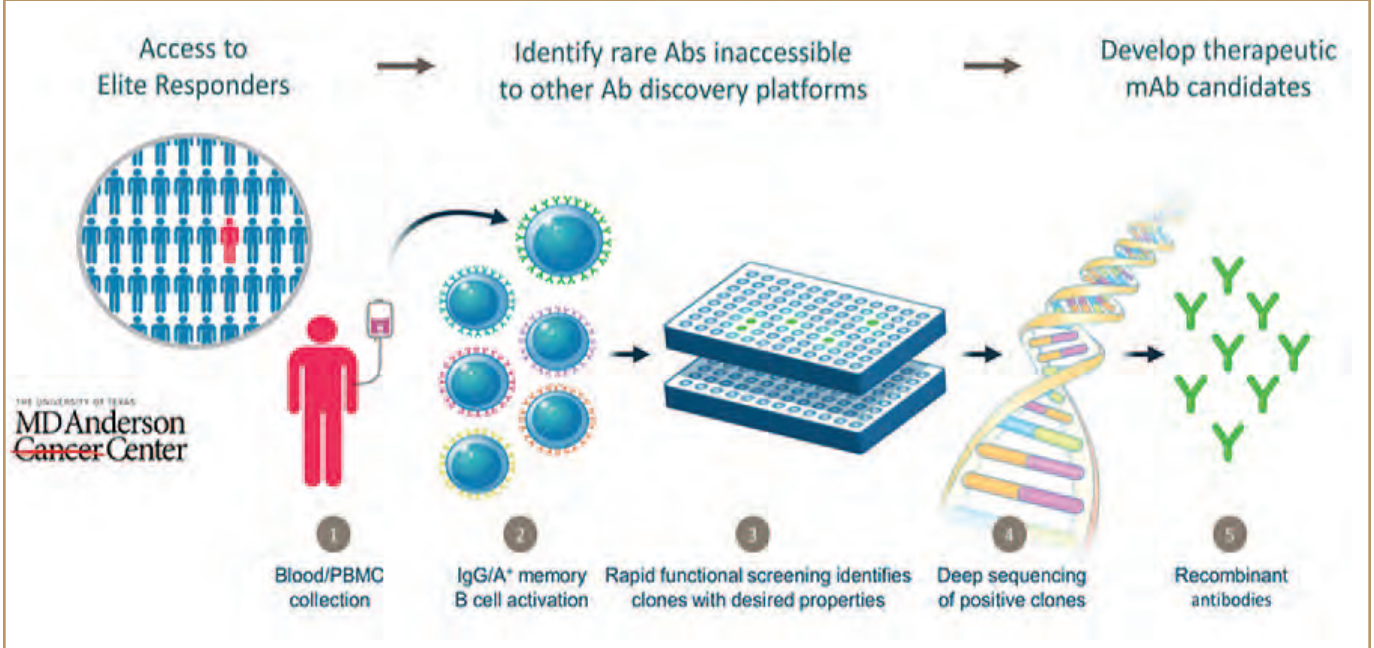
The incorporation of CPIs into standard therapy has significantly changed the cancer treatment landscape. Used alone, the best observed response rates (that is reduction in tumor volumes) hover around 35%, and while many patients are living longer, most are not cured of their disease. Much has been learned about the intrinsic determinants of response or resistance, centered on the understanding that tumors that have an already active immune tumor microenvironment (TME), with active infiltration of T cells (so-called "hot" tumors) are most likely to respond, whereas those that lack such infiltration (so-called "cold" tumors) are less so.[2] Central to the immunosuppression within the TME are tumor-associated macrophages (TAMs), which produce cytokines and other factors that foster an immunosuppressive environment and prevent the full activation of T cells following CPI therapy. OncoResponse set out to use our proprietary technology to identify targets on TAMs that could be manipulated to reverse this immunosuppression and promote the immune system's ability to efficiently kill tumor cells and enable clinical responses.

FOCUSING ON "ELITE RESPONDERS" TO CANCER IMMUNOTHERAPY

Our hypothesis was that patients who have exquisite responses to CPI therapy — we call these patients Elite Responders — have autoantibodies that help activate other components of the immune system and potentiate their response to CPIs. It is well known that cancer patients have a reduced self-tolerance and can produce autoantibodies to self-antigens. We thought to use this disruption of normal immune tolerance to identify antibodies made to normal proteins that might have a regulatory or immunostimulatory effect. In particular, we focused on TAMs, those key regulators of immunosuppression in the TME, looking for autoantibodies made by Elite Responders that could help reverse the immunosuppressive activities of these cells.

Macrophages in the TME exist in two broad categories: immunoinhibitory (called M2 macrophages) macrophages and immunostimulatory (or M1) macrophages. The majority of TAMs are M2 macrophages, which leads to immunosuppression in the TME. Using samples from Elite Responders, we looked for antibodies that bound to M2 macrophages, but did not bind M1. The ultimate goal was to identify an antibody that had a regulatory

FIGURE 1



Schematic of the OncoResponse discovery platform. B cells from samples obtained from Elite Responders are grown at clonal density in high-throughput plates and supernatants from individual wells screened for functional activity. B cells from positive wells are sequenced and the sequences used to develop potential therapeutic antibodies.

effect on TAMs that could reprogram them to be more M1-like.

One of the most difficult things to do in oncology drug development is obtain samples from patients with a specific treatment history outside of a sponsored clinical trial. When OncoResponse formulated the strategy to look for rare regulatory antibodies using our platform, it quickly became clear we would need a reliable source of high-quality samples, in particular serum and whole blood, to screen for potential hits. Our best chance of finding interesting autoantibodies would be to use samples from patients who had had exquisite responses to CPI therapy. So, we sought samples from patients who had partial or complete tumor reduction that lasted a minimum of 3 months. The key breakthrough came when we partnered with MD Anderson Cancer Center to identify such patients and rapidly obtain the necessary samples. We were able to negotiate a collaborative agreement that gave us access to numerous patient samples with minimal regulatory hurdles. Through this collaborative framework, we were able to screen sufficient samples for our lead generation.

A NEW APPROACH TO DISCOVER CANCER THERAPEUTICS

Human memory B cells are specialized lymphocytes that produce antibodies. Each B cell produces a monoclonal antibody to a specific antigen. Identifying a B cell that produces a particular antibody allows identification of the sequence of that antibody and subsequent production in a laboratory or commercial setting. OncoResponse's proprietary technology allows us to culture human B cells at clonal density, allowing identification of antibodies that are produced by a particular memory B cell. We can use the supernatants (ie, the monoclonal antibodies) from these cultures to screen against a protein or cell type of interest, looking for those B cells that produce antibodies that might modulate the response to cancer immunotherapies.

We began by screening serum from Elite Responders looking for antibodies that bound to M2 TAMs. B-cell cloning and production is resource intensive and first screening serum from Elite Responders against the selected target allowed us to narrow down the number of patients from whose blood we needed to grow B cells. After identification of patient serum samples that were positive hits, that is, contained pools of antibodies that bound to M2 macrophages, we went back to whole blood samples from these patients and cultured B cells for subsequent screening in the same assay. B cells were grown at clonal density, and supernatants from these cultures were then used for screens for activity. We confirmed binding to M2 macrophages and lack of binding to M1 macrophages, and also looked for functional activity. One of the key advantages

of the OncoResponse platform is the ability to identify functionally active antibodies early in the screen. Using the appropriate functional screen, in this case the ability to repolarize M2 macrophages to a more M1-like phenotype, we were able to identify antibodies with appropriate functional characteristics before we even knew the target of the antibody. In this way, we could reverse engineer an antibody that we know already has potential functional characteristics derived from a patient who experienced an exquisite response. Presumably, such antibodies were either present before treatment or were newly generated following the initiation of therapy. While we first targeted M2 macrophages in this screening campaign, we can use the same technology to look for targets on other cell types that may regulate responses to therapy.

Following identification of the appropriate B cell clone, deep sequencing can identify the sequence of the target antibody. In the case of multiple clones in one well, that is that more than one memory B cell was present in the original well, further experimental validation is required to identify the proper clone. To do this, we deep sequence the immunoglobulin heavy and light chain sequences and engineer the possible combinations. We can then test these in our functional assays to identify the correct combination that mimics the effects we saw in the original assays. After the right sequence is identified, cloning into a consensus vector for production and further characterization allows for rapid characterization.

A salient feature of this process is that functional antibodies, which might not be identified through conventional antibody development methods, are rapidly chosen. A hypothetical example of the advantage of this system may be seen if looking for an antibody that acts as an agonist to a receptor. In our functional screening technology, only antibodies that are activating for the receptor would be identified. On the other hand, conventional phage display or murine technologies will produce antibodies against any antigenic epitope, which must then be screened. If the activated conformation of the receptor is not easily replicated in the screening system, it may be impossible to identify an activating antibody. Similarly, if the epitope to be targeted is poorly immunogenic, or masked, or requires a conformational change, it may not be identified through conventional techniques. Because we screen for functionally active antibodies, we can identify and clone antibodies to unique epitopes that are immediately relevant and not easily amenable to targeting by other methods.

TAKING THE RESPONSE BACK TO PATIENTS

OR2805 was cloned from our original screen of Elite Responders looking for antibodies that targeted M2 macrophages. Biochemical and biophysical experiments identified the target of OR2805 as CD163.[3] At first blush, CD163 is not an obvious target. CD163 is a well-known macrophage scavenger receptor that has as its normal role to bind the hemoglobin-haptoglobin complex and clear this from circulation. CD163 is known to be upregulated on M2 macrophages and is considered a marker for such macrophages in the TME. OR2805 was found to bind to CD163 simultaneously in two separate domains of the molecule and likely induces a conformational change in the molecule leading to downstream effects that fundamentally reorient the functional status of the macrophage. This surprising observation suggests that the mechanism of action is not simply blockade of normal ligand binding, but a new and unique function of CD163 that could only have been identified by a functional screen such as the one we performed.

Extensive characterization of the interaction of OR2805 with CD163 demonstrates that it can potently reverse the phenotype of M2 macrophages. We have demonstrated that incubating M2 macrophages with OR2805 causes them to decrease expression of cell surface markers for M2 macrophages and increase those for M1 macrophages. The most important data, however, are the effects that OR2805 has on T-cell activation by macrophages. When T cells and M1 macrophages are co-cultured and the T cells stimulated by activation of the CD3 receptor, markers of activation such as the cytokines IL-2 and interferon gamma are produced and the T cells proliferate. In the presence of M2 macrophages, this activation and proliferation are prevented. When M2 macrophages are treated with OR2805, however, the phenotype is reversed, and robust activation and proliferation are observed. Finally, we have tested OR2805 in a mouse models of lung cancer. In these models, we used pembrolizumab (which is marketed for treatment of certain cancers as Keytruda®) as the gold standard for comparison. OR2805 demonstrated anti-tumor activity in these models that was equal or superior to that observed with pembrolizumab. Taken together, these data formed the basis of our IND and entry into the clinic.

OR2805 is now in Phase 1 clinical testing at multiple sites in the US. This rep-

resents the full circle of discovery and development, from the patient to the lab and back into clinical testing. The ability to identify functionally important antibodies produced by cancer patients responding to CPI therapy is a novel and powerful tool for the development of new therapeutics. While OR2805 is the first such therapy to enter clinical testing, no doubt other antibodies that can potentiate the response of standard-of-care therapies or induce responses on their own await discovery. Although macrophages play an important role in immunosuppression in the TME, other cell types contribute, and novel targets and mechanisms of action also await discovery. By applying our patient-first technology and looking for clues in the immune system, we can harness a powerful tool — the human body — to identify and produce new molecules to make medicines for cancer patients.◆

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BIOGRAPHY

Dr. Bob Lechleider joined OncoResponse from Seattle Genetics, where he was Senior Vice President of Clinical Development and was responsible for directing development of the early and late-stage portfolios, including the successful initial licensing of Padcev for the treatment of previously treated metastatic urothelial cancer. Prior to his work at Seattle Genetics, he held key roles with increasing responsibility at several biopharmaceutical companies, including MacroGenics, Human Genome Sciences, and MedImmune/Astra Zeneca. Before joining the biotechnology industry, he served as Assistant Professor of Pharmacology at the Uniformed Services University of the Health Sciences, and Associate Professor of Cell Biology at Georgetown University Medical School. He earned his AB cum laude from Princeton University and his MD from the University of Illinois College of Medicine at Chicago. He received clinical training in internal medicine at Beth Israel-Deaconess Medical Center in Boston and in medical oncology at the National Cancer Institute in Bethesda. He was also a Howard Hughes Medical Institute Scholar and a Damon Runyon-Walter Winchell postdoctoral fellow.

Special Feature

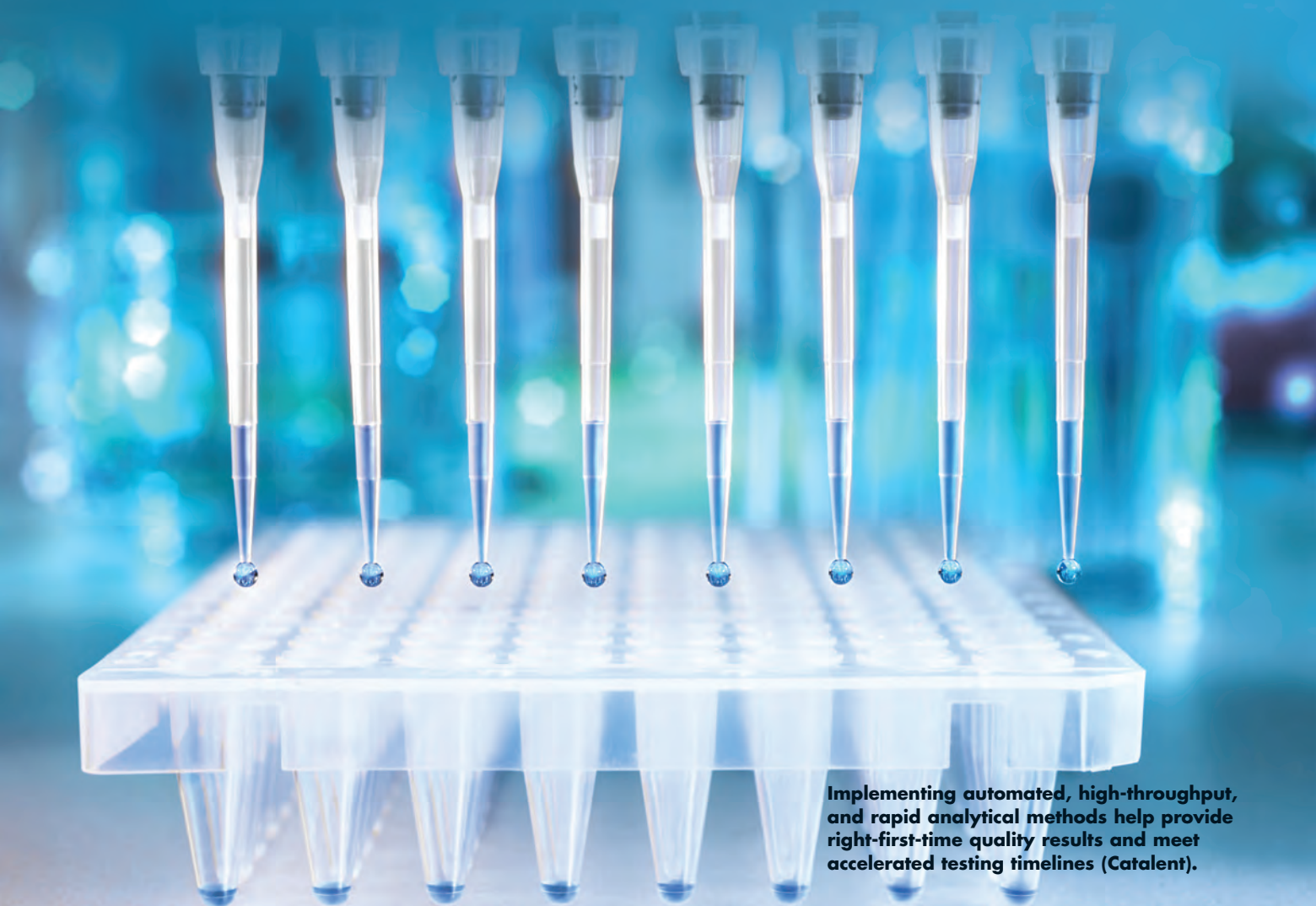
Outsourcing Analytical Testing – Faster Timelines & Quality Results at Reduced Costs

By: Cindy H. Dubin, Contributor

During the COVID-19 pandemic, many pharmaceutical development projects were delayed or postponed due to lack of available resources within analytical labs, as well as an inability to execute clinical studies. This has had a lasting impact on the industry as the desire to catch up to delayed timelines has driven the demand for more rapid and efficient analytical testing, says Michael Markham, Associate Director of Analytical Sciences at Adare. As a result, many organizations have turned to outsourcing some or all their analytical testing requirements to contract analytical testing laboratories.

This is why experts predict the global pharmaceutical analytical testing outsourcing market size to reach $14.6 billion by 2030.[1] Other drivers include increasing biological candidate pipelines, rising demand for additional analytical details on drugs, and process development by regulatory agencies.

Demand for bioanalytical testing services is expected to advance the fastest over this decade, as the legislation for *in vivo* and *in vitro* tests is changing and their complexities are increasing. The biopharmaceutical category will likely witness the fastest pharma-



Implementing automated, high-throughput, and rapid analytical methods help provide right-first-time quality results and meet accelerated testing timelines (Catalent).

ceutical analytical testing outsourcing market growth attributable to the high level of testing required for the validation of the efficacy and safety of bio-based drugs. Additionally, analytical testing majorly seeks to validate the bioavailability, pharmacokinetics, bioequivalence, and pharmacodynamics of the medication, all of which are mandatory before the drug can receive the marketing approval.[2]

In this exclusive *Drug Development & Delivery* annual report, leading contract development and manufacturing organizations (CDMOs) discuss not just their analytical service offerings, but their strategies for meeting regulatory challenges and ensuring faster project timelines.

Adare: Analytical Labs Require Experience & Knowledge

A successful pharmaceutical development project requires teamwork, constant communication, understanding of analytical results, and shared goals between the CDMO Formulation and Analytical departments. This important interaction and project understanding can be lost when the analytical testing is outsourced, causing delays or unusual results. Additionally, many contract analytical labs have staff retention issues. There are many reasons for this, including long hours and low pay for analysts at these sites, resulting in high turnover rates. The turnover can impact the experience and knowledge level available at a contract analytical lab, and is often below the experience and knowledge level at the CDMO. This can lead to mistakes and contribute to the overall lack of understanding of the data generated.

Adare has experienced this lack of understanding and experience at contract analytical labs. One specific example is when a project sponsor provided dissolution methods previously developed by a contract analytical lab. The method showed highly variable results with most batches exhibiting Stage 2, Stage 3, and even failing dissolution results with the method, leading to delays and inefficient testing, describes Michael Markham, Associate Director of Analytical Sciences at Adare.

At Adare, the dissolution was visually monitored by both the analytical scientist and the lead formulator. It was determined that the specified capsule sinker was too intrusive and, coupled with a low paddle stir rate, was causing incomplete rupture or dissolution of the gelatin capsules during the 30-minute run time. This caused some of the powder in the capsule to be shielded from the dissolution media by the partially dissolved capsule shell. Adare quickly solved these issues for the project sponsor.

Ascendia Pharmaceuticals: Developing Chemistry For – And With – Clients

Ascendia foresaw the increase in clinical trials coming and proactively started expanding its clinical trial material manufacturing and testing capability. During the year, Ascendia has more than doubled its physical footprint and has added both analytical testing and clinical manufacturing space, explains Muhammad Asif, PhD, Executive Director, Analytical R&D and Quality Control, Ascendia Pharmaceuticals.

Ascendia's specialization injectable suspensions prompted the addition of more advanced analytical instrumentation, such as Nanocam, that not only measures particle size distribution but also provides information about particle shape and morphology by taking pictures/videos. In addition to particle size, the particle shape, morphology, and degree of agglomeration also have direct impact drug bioavailability. Monitoring and controlling these parameters may help make a drug effective which otherwise passes through the body without absorption.

Being a developer and manufacturer of suspension and emulsion products, Ascendia has expertise in *in vitro/in vivo* comparison and equivalence, says Dr. Asif. "Ascendia designs *in vitro* studies to provide a view into what is expected from *in vivo* studies, resulting in significant time and cost savings," he says.

For example, an extended-release product in which a single dose or injection is efficacious for up to 3 months not only translates into cost savings but also ensures better patient compliance. Dr. Asif says that, for such products, *in vitro* studies are performed for days or even a week so that they can predict and mimic the *in vivo* bioavailability profile. After the product development is complete, Ascendia designs faster quality control methods that ensure the product properties stay the same from batch to batch. "This approach not only reduces product development time and cost, but makes the product more affordable when it is marketed," he says.

Faster development timelines require smart Design of Experiments (DoE) and state-of-the-art instrumentations and methodologies. "Instrumentation like Nanocam that provides information about multiple parameters in one experiment goes a long way in reducing time and resources, resulting in cost savings," he says. "Ascendia passes on such savings to our clients, which in turn, pass onto patients."

In fact, Ascendia's goal is to develop products that can be affordable by the

Ascendia Pharmaceuticals Senior Scientist Xinyu Wang, PhD, analyzes an under-development suspension parenteral drug product using a Flowcam Instrument that concurrently provides information about particle size distribution, particle shape and morphology, and degree of agglomeration.

maximum number of patients, says Dr. Asif. "When a potential client visits Ascendia, the first thing we communicate to them is that we are their product development team. Our clients will testify that they feel like Ascendia is just like their internal R&D group because there is frequent, open, and honest communication between the two operating teams. Ascendia's size and cooperative culture help to develop chemistry with our clients."

Catalent: Service That Goes Beyond Standard Testing

Over the past year, Catalent has been expanding its analytical laboratory capacity and capabilities at both its global manufacturing and standalone analytical facilities. These expansions include investing in equipment to meet the additional analytical needs of advanced therapies, such as viral vectors, cell therapies, mRNA, and protein therapeutics, while hiring and developing the talent necessary to address the scientific challenges of biologics, explains Emily Magner-Fink, Director, Commercial Operations, Catalent Bioanalytical Services.

Additionally, to meet partners' accelerated timelines, Catalent is implementing automated analysis, high throughput, and rapid methods wherever possible, and is continually evaluating new, multi-purpose instruments that can provide more data from a reduced sample size. Controlling the post-pandemic material supply chain also remains key to providing timely results. "The company strives to ensure 'right-first-time' results, streamlined workflows, and flexible resourcing to meet evolving client demands," she says

Catalent also employs a global network of analytical laboratories to support increasing customer demands, adds Jeff Schwartzenhauer, ARD Group Leader, Catalent Windsor, Ontario. "By connecting scientists across this network, the best expertise, capabilities, and capacity can be made available to support customers' programs."

Ms. Magner-Fink and Mr. Schwartzenhauer say that Catalent's clients often face two major issues when outsourcing: an inability to find a single provider that can support their entire panel of analytical testing; and the provider not having the resources or expertise to develop and validate cell-based potency assays. Bioassays can be challenging to develop, particularly when needed for GMP release and stability testing. They say that Catalent can perform a range of analytical assays and has the scientific expertise to provide support for bioassays from clinical through to commercial phases. "We develop assays utilizing the latest technologies, such as automated sample preparation and single-use thaw-and-go-cells to ensure consistent performance," says Ms. Magner-Fink. "This has allowed many customers to reduce the number of suppliers to manage, streamline workflows, and ensure the clinical and commercial success of products through phases of development."

Mr. Schwartzenhauer adds that Catalent has expertise and knowledge to design studies that can assist in choosing the appropriate testing for long-term evaluation of products. "Our willingness and ability to think beyond standard approaches has resulted in long-term reductions in costs and timelines for our customers by ensuring that the correct testing programs are chosen for an individual project rather than just a standard range of tests."

PCI Pharma Services: Meeting Timelines for Sponsors & Patients

As a global CDMO, PCI Pharma Services provides integrated end-to-end solution to support the drug product lifecycle from development to commercialization of both sterile and non-sterile dosage forms. Mindy Gagnon, Senior Director Quality, says that PCI's dedicated in-house analytical testing capabilities ensure incoming drug substance and raw materials are

tested upon receipt and are readily available for processing, methods can be developed and validated quickly, and finished drug product is released to clinic or market supply in a timely manner.

"Meeting the increasing needs of our clients for speed to patient, we continue to invest in our global analytical laboratories, increasing our expert analytical scientist headcount together with investing in new technologies and LIMS (Laboratory Information Management Systems)," she says. "Reducing timelines and complexity, our advice is to validate analytical methods following a phase-appropriate approach. If regulators request additional data, then this can be supplemented at a later date. This means the focus can be centered on critical analytical activities to increase the speed of drug to patient."

Ms. Gagnon says that PCI continually evaluates and expands its testing capabilities in line with the growing needs of its clients. "If testing internally does not align with our customers' analytical needs or timelines, we can utilize our strong network of third-party approved laboratories. These partnerships are robust and allow us to provide flexible services to meet the most aggressive and challenging analytical asks."

PCI's analytical testing services are built to be flexible and support a variety of different analytical needs. She says: "Having internal GMP Analytical Services laboratories housing both Analytical Development and Quality Control means formal method transfers from one department to another is not required. This is a major benefit for our client partners as it removes the need for additional analytical transfer work, reducing the risk of loss of knowledge between laboratories reducing cost and timelines."

Pii: Faster Analytical Testing Requires Better Communication

Pii's analytical laboratory is USFDA-approved, providing customers with analytical testing support for CMC and commercial activities, as well as early- to late-stage development. Pii is also working towards establishing capabilities to support chemical testing for biosimilars/biologics.

Pii has also reinvented and aligned its business plans to address the demand and importance of analytical testing needs in the COVID-19 era for efficient and faster drug research and development processes. This has resulted in a redesigned business model that now encompasses standalone analytical testing services.

"Pii has focused on accurate, faster, and quality results and built a team accordingly that can deliver such fast-paced needs of pharma companies," says Rahul Mehta, Associate Director, Pii.

Pii has established a tool where its customers can discuss their technical needs directly with the Pii technical team, which gives additional benefit and opportunity to explain their need with clarity. This, he says, will help to produce error-free results and hasten the process.

Mr. Mehta advises that when outsourcing analytical testing, a lack of information is a common root cause for delay and failure. "If you need faster support for any analytical testing, it is important to provide substantial information and background for the testing," he says. "And, if additional information can be shared with the outsourced laboratory, this will result in better understanding and clarity to perform the testing (such as the stage of the product, purpose of testing, use of testing, urgency of testing, history behind any testing, etc.). This can help the outsourced lab to eliminate any avoidable issues and produce faster and accurate results."

SGS: Helping Clients Reach Global Markets Quickly & Safely

Now more than ever, technological advancements, regulatory requirements, and turnaround times are some of the biggest drivers for outsourced analytical testing. Companies rely on SGS to help them navigate the changes in technology and the complex global regulatory landscape throughout their accelerated journey to market, says Niveen Mulholland, PhD, Vice President SGS Drug Development North America.

This is particularly true for biosimilars, as well as specialized biologics products,

A Pii scientist installing an HPLC column.

such as cell and gene therapies. SGS has witnessed manufacturing advances, including enhancements in yield and purity, innovative cellular production systems, and novel delivery systems that in turn, drive the testing needs. These advancements require strong technical support and expertise as well as analytical method development and routine QC testing, says Dr. Mulholland.

Within its network of GMP laboratories, SGS has established a number of platform methodologies that can be applied directly, or with minor modifications, which supports the next generation of biosimilars.

Dr. Mulholland says that the pandemic transformed speed-to-market demands, forcing SGS to develop agile ways of working to optimize for speed and improved decision making. "SGS has focused on digital technology and workforce agility to address our clients' needs for faster turnaround times," she says. "We have made investments in automation of highly repetitive processes and digital enablement of faster access to data."

The success stories that tend to be the most exciting for SGS are the ones where its teams have played a pivotal role in supporting a successful IND submission for a new drug or therapy – a critical step in gaining FDA approval for allowing a drug to be tested in humans. "Biopharmaceutical companies in the cell and gene therapy space have been relying on us to develop technically complicated methods and perform testing under strict timelines, which is particularly critical for this highly competitive market."

One recent example is the analytical support SGS provided to a gene editing company. "We were able to qualify the necessary assays for their flagship product in a timely manner to meet the filing deadlines for their first IND," says Dr. Mulholland. "The client acknowledged that the achievement of this important milestone would not have been possible without the services and expertise provided by SGS."

Triclinic Labs: Choosing a Provider is About More Than Price

Triclinic Labs offer scGMP and non-cGMP testing for a variety of identification, quantification, and CMC testing needs. This allows clients the flexibility to determine what is necessary (and required) at any given point in development, says Aeri Park, PhD, Chief Scientific Officer at Triclinic Labs. She says non-cGMP testing usually affords up to 30% faster and less expensive testing than cGMP. "We also offer different service levels with turnaround as fast as 24 hours for many tests – for cGMP testing we can accommodate 48-hour turnaround, including release testing." Triclinic Labs has broadened its testing at the request of clients and has added ICP-MS, LC-MS-MS, and both solids and liquids NMR with an auto-sampler to accommodate batch testing.

All of Triclinic Labs' instruments are latest generation and have redundancy for nearly every system, Dr. Park continues. The CDMO has a DEA schedule I-V registration, allowing Triclinic Labs to accept any asset in development and to handle potent compounds. "Our facility is registered and inspected by the FDA (historically no findings, no 483s)."

Dr. Park says one area where Triclinic Labs has seen a significant increase in is requests for development and validation of testing methods. As more manufacturing has been domesticated to provide better supply chain continuity, more release tests are necessary to ensure consistency and quality in manufacturing – not only drug substance, but drug product, she says. "Thus, we have added staff and new instrumentation to accommodate these requests and to ensure faster development and the ability to accurately and safely release pharmaceuticals for human consumption," she indicates.

Dr. Park says that many labs can offer fast analytical testing, but few offer orthogonal testing as well as interpretation of data for actionable results. "Most clients

Andy Smith of Triclinic Labs awaits results of thermal and spectroscopic analysis of samples.

come to Triclinic because they are experiencing an issue in development or manufacturing and need to solve a problem," she says. "Having a lab that looks at the problem holistically and offers a path to solve the issue supersedes the desire for a cheap test and a piece of data."

West Analytical Services: Modeling System Makes Evaluations Early in Development

While there is an emphasis on R&D to move quickly and efficiently especially with biologics, there are still the regulatory guidelines and industry expectations such as the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA) in the European Union, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan that need to be considered when developing your drug product. Customers must balance developing quickly while still capture data that supports their decisions for primary packaging. Part of that process is selecting the primary packaging for the drug product that provides adequate protection against deterioration or contamination of the drug product and maintain sterility through its shelf life.

For biologics, many are continuing to use vial, stopper and seal systems. In order to make an educated system selection early in the drug development process, West has developed the DeltaCube™ Modeling Platform. The DeltaCube™ Modeling Platform allows customers to rapidly evaluate the fit of multiple vial containment systems using actual component data rather than only the drawing specifications. "This means that rather than using two points of theoretical data, you use data from the life of the West or Daikyo

product," explains Anthony Bucci, Principal Engineer, Scientific Affairs, West. "The DeltaCube™ Modeling Platform also allows you to upload your own data. You can model different stopper compression ranges and seal skirt length to see how theses variable impact your system fit and help optimize your operating range."

Based on the outcome of the model created, users can select the vial system with the best fit for their drug product, which reduces time for vial system evaluation, and decreases the time to use a fill/finish line for testing samples, which saves money in the long run, he says.

As the next step in this process, West Analytical Services provides container closure integrity testing following USP <1207> deterministic methods to provide the data to support your vial system selection giving you a complete picture of your vial system fit-for-use.

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Drug Development
EXECUTIVE

Bryan Kobel

CEO

TC BioPharm

TC BioPharm: Developing Platform Allogeneic Gamma-Delta T Cell Therapies for Cancer

TC Biopharm (Holdings) PLC (NASDAQ: TCBP) (NASDAQ: TCBPW) is a clinical-stage biotechnology company developing platform allogeneic gamma-delta T cell therapies for cancer. Established in 2013 and based in Scotland, TC BioPharm is currently conducting its Phase 2B trials of its proprietary therapeutic, OmnImmune®, an allogeneic unmodified cell therapy consisting of activated and expanded gamma delta T cells. The trial is for the treatment of patients suffering from relapse/refractory Acute Myeloid Leukemia (AML).

OmnImmune comprises gamma-delta T cells sourced from healthy donors, expanded, and activated in large numbers before being purified and formulated for infusion into patients. It is a frozen and thawed allogeneic product, now "banked" from donor derived cells.

Gamma-delta T (GDT) cells are naturally occurring immune cells that embody properties of both the innate and adaptive immune systems and can intrinsically differentiate between healthy and diseased tissue. The GDT cells are activated via their T-cell receptor (TCR) after recognizing molecules that are only present on stressed, virally infected or cancer cells. The activated GDT cells can then use a variety of mechanisms to kill cancer cells and virally infected cells. This includes direct killing via perforin and granzymes, or indirectly through cytokine production. The molecules, which activate GDT cells, are shared by a variety of stressed and tumor cells, making it possible for GDT cells to target a broad range of different tumors. TC BioPharm uses an allogeneic approach in both unmodified and CAR-modified gamma delta T cells to effectively identify, target, and eradicate both liquid and solid tumors.

TC BioPharm is the leader in developing banked allogeneic gamma-delta T cell

therapies, and the first company to conduct International Conference on Harmonisation (ICH) compliant Phase 2/pivotal clinical studies in oncology. Previous clinical results have enabled TC BioPharm to obtain FDA orphan drug status for its method of treatment of AML. Orphan drug status is a designation granted by the FDA for therapies targeting rare diseases. The status allows for a 7-year exclusive marketing window post approval of the drug, certain lowered application fees and tax incentives.

The company's primary goal is to develop safer, less-expensive CAR-T products that can target a broad range of cancers and save more lives. TC BioPharm does this using its integrated model that drives the development of products through preclinical testing to the clinic.

Drug Development & Delivery recently interviewed Bryan Kobel, CEO of TC BioPharm, to discuss the company's upcoming plans, therapeutic, clinical trials, and the biotech landscape.

Q: What are gamma-delta T cells, and what is their role in supporting our immune system?

A: Gamma-delta T (GDT) cells are a functionally distinct component of the lymphocytes (white blood cells) present within all humans, representing approximately 1%-5% of the circulating population. They are naturally occurring immune cells that embody properties of both the innate and adaptive immune systems and can intrinsically differentiate between healthy and diseased tissue. Tumor recognition and killing is not dependent on the expression of a single antigen, therefore enabling GDT cells to recognize a broad spectrum of antigens on different cancer cells. GDT cells have been termed "unconventional" T cells as they recognize different antigens without presentation by Major Histocompatibility Complex (MHC) molecules. Given their ability to bridge the innate and adaptive immune system, GDT cells have been shown to play a key role to interact directly and indirectly with different immune cells to orchestrate the immune response. As part of the immune system's innate and adaptive response, their natural properties make them promising therapeutic candidates.

Q: How is TC BioPharm using gamma-delta T cell therapies for the treatment of cancer?

A: GDT cells constantly monitor the body for signs of biological stress, such as cancerous or infected cells, and are one of the first lines of defense against disease. TC BioPharm's therapies are focused on leveraging the inherent biological capabilities of GDT cells together with an integrated cell engineering approach.

TC BioPharm collects cellular material from healthy donors as a source to manufacture next-generation allogeneic "off-the-shelf" GDT cell therapies for clinical development. To achieve this, we currently use a proprietary media formulation to support the selective expansion of unmodified and CAR GDT cells. This media yields a high number and high purity of GDT cells at the end of the expansion process. Our cell banks have enabled the generation of cost-effective, safe, and efficacious therapeutic treatments that allows us to treat more patients.

OmnImmune is our unmodified allogeneic GDT cell product, being initially used for the treatment of AML, aiming to treat patients who have not responded well to first-line therapy and preventing the need for a bone-marrow transplant.

Q: You recently initiated Phase 2b/3 gamma-delta T cell therapy clinical trials of OmnImmune. Can you discuss the early results?

A: The early results are very encouraging. We have positive safety findings from the first cohort of the clinical trial; the drug was well-tolerated and safe in R/R AML patients, with no dose-limiting toxicities. Furthermore, no signs of acute or chronic graft-versus-host disease (GvHD) nor organ injury were reported. Preliminary safety data shows that our allogeneic cell therapy is safe and well-tolerated, which has enabled the company to progress OmnImmune to Phase 2b/3 clinical trials.

Q: TC BioPharm went public in February of this year. What are your goals as a public company?

A: Our key goal as a public company is to gain more access to capital to help expedite the next phase of our clinical trials and bring OmnImmune to market. We believe this is a truly revolutionary product that will positively impact not only AML

treatment but cancer therapies in general.

We also have stealth programs being developed for additional next-gen cell therapy treatments. The capital from going public will help our extremely talented and dedicated staff to develop these treatments.

Q: Can you expand on the opportunities there are to using combination therapies/approaches with OmnImmune for the treatment of solid tumors?

A: A number of other companies have recognized the huge potential of GDT in cancers and are developing non-cell-based therapeutic approaches to enhance GDT function for the treatment of solid tumors. Our therapeutic approach is based upon the infusion of a healthy effector population of GDT and CAR-GDT cells into the patient to target and eradicate the tumor. Our clinical experience has demonstrated that GDT populations in patients with late-stage disease are anergic and exhausted. An opportunity therefore exists as a combination approach to combine these non-cell-based approaches with OmnImmune to augment the clinical response.

In addition, we have a number of in-house and partner programs at the preclinical stage focused on developing CAR modified allogeneic gamma delta T cell products targeting solid and hematological indications.

Q: What are the key trends you are seeing in the solid-tumor CAR-T therapy space?

A: Chimeric antigen receptor (CAR) T cell therapy has made an impact on the treatment of certain blood cancers. Previously, in many clinical studies, the cellular therapy was not as successful for patients with solid tumors. A number of challenges remain for the treatment of solid tumors, including CAR-T function on the immunosuppressive tumor microenvironment, identification of CAR targets selectively expressed on the tumor, lack of tumor target expression in target tissues, CAR T cell trafficking, tumor infiltration, and persistence. The other issue with standard CAR T-cell therapies has been on-target, off-tumor toxicity caused by CAR antigen expression on normal calls.

Different CAR-T approaches are currently under active investigation by CAR-T companies to address these challenges. Today, we are seeing them branch out aggressively into solid tumors as the efficacy data rolls in, especially the gamma-delta companies. Several of these companies are using different CARs to enhance the cell therapy in their indication of choice and can do so while still showing very little of the previously associated toxicity with CAR technologies. There are many CAR-T approaches targeting solid tumors in early clinical development, and many of these are addressing key challenges, such as infiltration, persistence, and exhaustion. It is an exceptionally exciting time to be developing next-gen approaches as we anticipate emerging efficacy data.

Q: Can you provide insight into next steps with OmnImmune and when it will be commercially available?

A: TC BioPharm plans to expand the Phase 2/3 study to the US in the fourth quarter of 2022 or early 2023. Currently, we are in conversations with the US FDA regarding the final trial protocol in conjunction with our US clinical partner. ◆

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FORMULATION DEVELOPMENT

Understanding CBD Formulation Versus Dosage Format

By: Gerry McNally, PhD

INTRODUCTION

There are many misconceptions when it comes to considering the best way or format to consume cannabidiol (CBD) and get the maximum benefit. Formulation scientists need to consider several factors when developing new formulations of nutraceutical ingredients, especially botanical ingredients and natural materials from various sources. One of the first considerations is the purity of the ingredient along with its physicochemical properties, such as solubility, density, flowability, and stability. Botanicals and naturally sourced ingredients are complex and often can contain multiple chemical components, not to mention several classes of compounds. The physical, chemical, and sensorial properties of botanical extracts from different sources can be remarkably variable, making it difficult to directly substitute one source for another in a finished formulation.

The properties of the botanical active can have a direct bearing on the type of dosage form into which it can be formulated. For example, if the ingredient is an oil or wax versus a water-soluble material, it may not be easy to formulate into tablets or capsules. Similarly, ingredients with a large serving size may have to be delivered as a powder that is mixed into water for easy consumption. Hemp extracts are a good example of botanical ingredients, where along with the major cannabinoid CBD, there may be some THC (<0.3%) and minor quantities of many other cannabinoids as well as terpenes and flavonoids. The lipophilic extracts pose significant formulation challenges that must be addressed so that a safe, efficacious, and palatable product is available for consumers. The efficacy of any supplement is based on a sound understanding of its bioaccessibility and, more importantly, bioavailability.

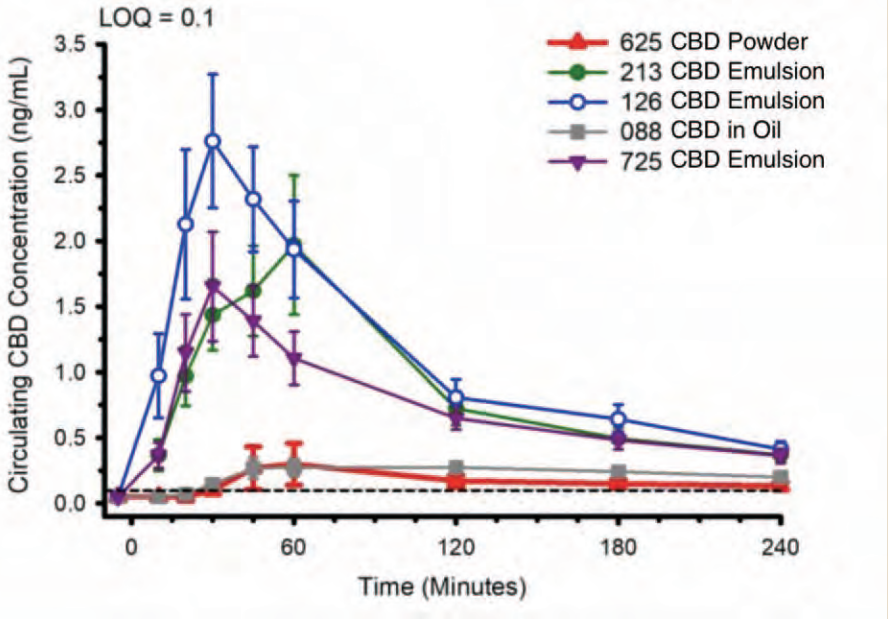
HEMP EXTRACTION & PURIFICATION

Cannabinoids are extracted from the hemp plant biomass in a series of steps involving solvent extraction, filtration, and finally distillation to arrive at CBD distillate. The distillate is then further processed to produce either full spectrum, broad spectrum, or isolated single cannabinoids. Reproducibility of the whole plant extracts or full spectrum products may be challenging because of the difficulty to control variables, such as harvest to harvest variation and extraction process or formulation differences.

So called "THC-free extracts" may contain some minor cannabinoids, terpenes, flavonoids, and other trace ingredients. Broad spectrum CBD has no THC but may comprise some minor cannabinoids and terpenes; however, there is no rigorous definition of what the composition should contain. Lastly, there is pure CBD often referred to as CBD isolate. Pure CBD is a white to off-white crystalline powder. CBD in its unpurified form (full spectrum or broad spectrum) may exist as a resin, wax, or oil, depending on what other plant constituents are present. From a consumer perspective, the unpurified CBD is typically dissolved in oils, such as medium chain triglycerides or other vegetable oils.

Recently, it has been reported the THC (a psychoactive cannabinoid) content of many CBD tinctures is much higher than expected. This can place consumers in the precarious position of being unexpectantly intoxicated or potentially failing drug tests.[1]

FIGURE 1



Cannabidiol and Cannabidiol Metabolites: Pharmacokinetics, Interaction With Food, and Influence on Liver Function[16]

BIOACCESSIBILITY & BIOAVAILABILITY

Understanding how the physicochemical attributes may affect the bioaccessibility and hence the bioavailability is also critical to developing and delivering a safe and effective dietary supplement.[2] Water-soluble components are easier to work with and can fit with a variety of delivery formats. Conversely, poorly soluble or insoluble ingredients present a significant challenge.[3,4] A particularly challenging subset of ingredients are fat-soluble or lipophilic materials that must be formulated carefully to attain optimal absorption. Bioaccessibility is the first step in the process of a compound or nutrient becoming bioavailable. In this step, the compound or nutrient is first released from the delivery system, which can be a food matrix such as a gummy, or a swallowed dosage form, for example, a capsule or tablet. Many digestive steps from chewing to mixing with acid and enzymes in the gastric juice are involved in the process of making bioactives and nutrients bioaccessible. Once released from the delivery format, the bioactive or nutrient should then be available to the body in a form suitable for absorption.

The oral bioaccessibility and bioavailability of lipophilic bioactives has been shown to be enhanced when the waxy or oily ingredient is formulated into an emulsion. The composition of said emulsion, ie, lipid and emulsifier types used, as well as the key physicochemical attribute of emulsion droplet size have a direct impact on the release from the dosage form. These attributes also have a bearing on the ultimate solubilization, transport, metabolism, and absorption in the gastrointestinal tract (GI) and can affect distribution to the lymphatic system.

It is clear from the work of Gershkovich et al that the lymphatic absorption of CBD is critical to attaining superior blood levels.[5-7] This is not unexpected given how other oily nutrients have been formulated.[3]

The absorption of many lipophilic nutrients and bioactives are affected by food intake, this is called a food-effect-related absorption factor. In multiple food-effect studies, it has been reported the amount of CBD absorbed increased approximately four-fold when it was consumed with a high-fat meal, compared to fasting conditions.[8]

FORMULATION OF CBD TO IMPROVE BIOAVAILABILITY

As previously mentioned, CBD, THC, and other minor cannabinoids are lipophilic compounds and hence need to be formulated appropriately to achieve reasonable levels of absorption especially via the gastrointestinal tract. This is important as most consumer CBD offerings are formulated as oral products either as tinctures, gummies, capsules, tablets, softgels, or in beverages. It has been shown that unformulated CBD has extremely low bioavailability (less than 5%), while dissolving CBD in oils such as the MCT or sesame oil can increase bioavailability to between 6%-13%.[9] The most significant increase in the bioavailability of CBD has been achieved when the cannabinoid has been formulated into a system in which the lipophilic material is encapsulated by hydrophilic ingredients. These formulations can involve various technical approaches, such as micro- or nano-emulsions, self-emulsifying systems, liposomes, micelles, or other complexes, such as those with beta cyclodextrins.[10] This may be achieved using natural ingredients and emulsifiers while some methods require inclusion of synthetic materials, such as some SEDDS (self-emulsifying drug delivery system) formulations. The CBD formulations with en-

hanced bioavailability are often referred to as water-soluble or water-miscible formats. There has been a considerable amount of preclinical and clinical research on how these emulsified formats enable superior cannabinoid absorption.[10-13] However, there is still work to be done to better understand the effect of emulsion droplet size and formula constituents on the bioavailability of CBD.[10,15]

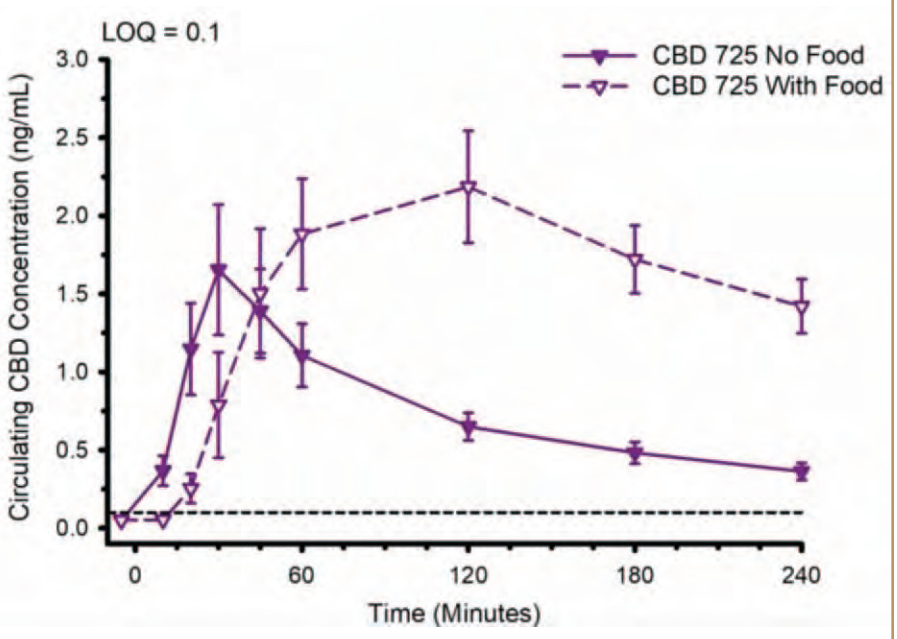
INCORPORATION OF WATER MISCIBLE CBD INTO FINISHED DOSAGE FORMS

Once the CBD or hemp extract has been successfully formulated to be more bioavailable, it must then be incorporated into a consumer-friendly delivery format consumers are familiar with, such as gummies, capsules, tablets, and powders.

It is important to recognize that oil-based CBD formulations, while normally being synonymous with tinctures or softgels, may also be incorporated into gummies and other edible formats. So, one should not equate the finished delivery format with any expected level of performance in terms of bioavailability. What is critical to achieving the optimal bioavailability is that the lipophilic cannabinoid material is first formulated into a composition that lends itself to being absorbed within the human GI tract. Some absorption-enhancing technologies are more flexible than others, ie, they are available in both liquid and solid formats, enabling the formulation of a wide variety of finished dosage forms.

When it comes to having confidence in the bioavailability of a CBD formulation, there is no substitute for human bioavailability data. There have been several human pharmacokinetic studies completed on commercially marketed consumer CBD products.[11,13,14,16]

FIGURE 2



Cannabidiol and Cannabidiol Metabolites: Pharmacokinetics, Interaction With Food, and Influence on Liver Function[16]

LEARNINGS FROM RECENT HUMAN PK STUDIES

In the past 3 years, several pharmacokinetic studies on commercial CBD formulations have been carried out by independent academic researchers.[13,14,16] The pharmacokinetic learnings from these studies are several. First, pure CBD powder or CBD dissolved in oils are significantly less bioavailable that emulsified CBD formulations, see Figure 1 taken from the recent pharmacokinetic study.[16] Second, for CBD emulsions the choice of the natural emulsifier as well as the emulsion droplet size can affect the bioavailability. Finally, it was found there is a noticeable increase in the bioavailability of emulsified CBD formulations when taken with food, see Figure 2 taken from the same pharmacokinetic study.[16] This outcome is not dissimilar to the food effect observed with oil-based solutions of CBD.[17,18]

CBD FORMULATION & DOSAGE FORM MISCONCEPTIONS

There are several misconceptions around CBD and the formats best suited to its administration; some of the major ones are discussed here. First, CBD is not an oil as has been widely reported in the media, rather it is a crystalline powder as mentioned earlier. Because of CBD's lipophilic property, it is soluble in many oils but not in water; this led to early formulations, such as oil-based tinctures or softgel capsules.

It has also been frequently communicated that CBD tinctures are absorbed in the buccal cavity or via sublingual administration. However, it is suggested that little if any cannabidiol is absorbed through the buccal mucosa.[19] The only instance in which sustained buccal delivery of a lipophilic active such as cannabidiol was

achieved was using an occlusive buccal adhesive patch technology.[20] The cannabidiol was reported to absorb into the buccal tissue and eventually achieved clinically relevant plasma levels; however, the rate was deemed to be relatively slow and not suitable for an immediate- release delivery system.

There has been a wide array of water-soluble or more appropriately termed water-miscible products entering the CBD market throughout the past several years. Claims that nano-emulsions or dispersions of one form or another have superior bioavailability have become commonplace. However, there is little in the way of preclinical or clinical testing in human subjects to support these claims. It may be possible there is an optimal sub-micron emulsion droplet size that results in improved bioavailable and that smaller is not always better.[21]

SUMMARY

Consumers seeking benefits from CBD and other cannabinoid products should look carefully at the formulation to determine which product may be best for them. The best scenario is that the manufacturer can refer to studies carried out on its products in a human population.

Many consumer CBD products refer to the number of milligrams of ingredient, which may lead consumers to believe that higher labelled levels of CBD will address their particular concerns. Recent pharmacokinetic studies have highlighted significant variance in CBD blood levels based on product formulation in which a properly formulated product can be several times more bioavailable than a simple oil-based solution. Selecting a CBD product on the basis of proven bioavailability rather than the number of milligrams listed per serving or per container may be a more reliable approach to achieving a satisfactory outcome. ◆

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BIOGRAPHY

Dr. Gerry McNally is a seasoned consumer healthcare R&D executive with more than 25 years of experience as an R&D leader in the consumer healthcare industry. During his tenure at McNeil Consumer Healthcare and Johnson & Johnson, he was instrumental in leading the development of numerous innovative and highly successful products and launching multiple novel drug delivery technologies. He was involved in creating unique formulations for Imodium® Multi-Symptom Relief, and Pepcid® Complete and novel formats, such as Tylenol® Rapid Release Gels. He earned his PhD and BSc Hons. in Chemistry from University College Dublin, Ireland. He holds more than 30 patents in the field of drug delivery/pharmaceutical formulation, has authored several papers, and delivered presentations at industry conferences.

THERAPEUTIC FOCUS

Addressing the Unmet Need for Improved Treatments of Female Cancers

By: Martin Lehr, MA

INTRODUCTION

Up to 70% of women with breast, ovarian, and endometrial cancer have hormone-dependent cancer.[1] The hormones estrogen and progesterone drive cancer progression in these patients, but antiestrogens are the only antihormonal therapy approved by the US FDA and available to clinicians. Treatment of these patients to date, therefore, has consisted of antiestrogens alone or in combination with drugs that enhance the antitumor activity of antiestrogens, including inhibitors of CDK4/6 or PI3Kα. Given the broad use of antiestrogens, antiestrogen resistance is now a major clinical challenge. Treatment options for antiestrogen resistance are limited, provide modest therapeutic benefit, and are associated with side effects.

Estrogen and progesterone are master regulators of normal female sex organ development and function, acting via estrogen receptors (ER) and progesterone receptors (PR). In hormone-dependent cancers, ER and PR are often hyperactive, constantly pushing breast, ovary, and endometrial tissues to grow, divide, and metastasize. To block this hormone-mediated growth, patients are administered antiestrogen therapy (fulvestrant, letrozole, anastrozole, or tamoxifen) alone or in combination with inhibitors of CDK4/6 or PI3Kα to block ER signaling. The cancer cells respond to this selective pressure of ER inhibition, however, by further activating progesterone signaling as a compensatory mechanism, along with other resistance mechanisms that can induce PR signaling, including ER ligand binding mutations (ESR1), growth factor signaling, and enrichment of cancer stem cells. Over time, all patients with advanced or metastatic disease eventually become resistant to antiestrogens due to direct or indirect compensatory signaling mediated by the PR and other factors.[2-4] Therefore, PR and proteins that regulate PR represent ideal drug targets to address antiestrogen resistance.

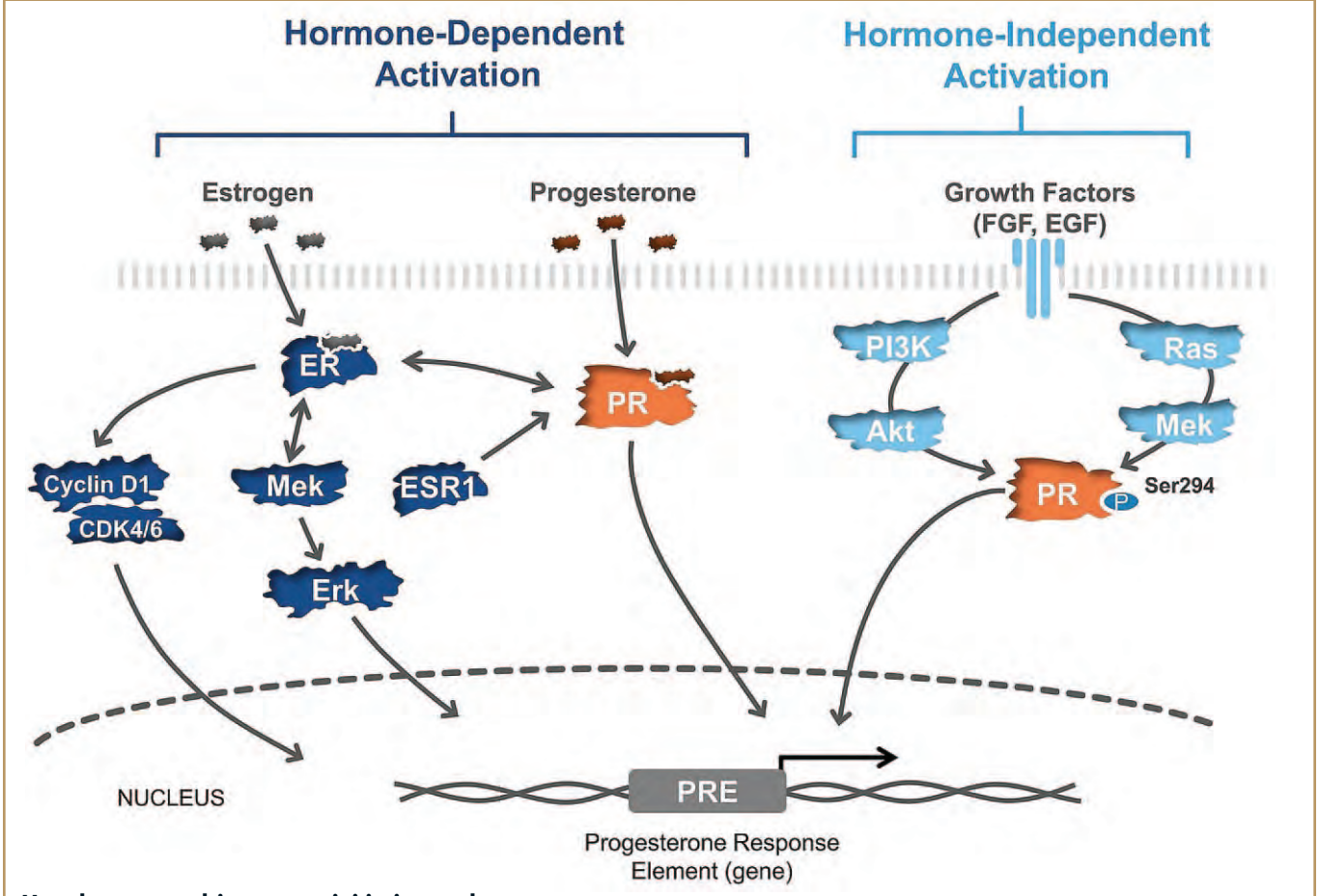
Context® Therapeutics (Context) is a clinical-stage biopharmaceutical company dedicated to improving the lives of women living with cancer. Our goal is to develop and commercialize innovative and differentiated oncology products that address significant unmet medical needs in the field of female cancer. Context is building a portfolio of novel agents targeting multiple resistance mechanisms by leveraging our specialized expertise in hormone-dependent cancers, with a pipeline spearheaded by our clinical-stage lead program, onapristone extended release (ONA-XR), a selective and potentially potent antagonist of PR.

Our second program is CTIM-76, an anti-CD3 x anti-Claudin 6 antigen bispecific monoclonal antibody (CLDN6xCD3 bsAbs), is in preclinical development. CTIM-76 is intended to redirect T-cell-mediated lysis toward malignant cells expressing Claudin 6 (CLDN6). CLDN6 is a tight junction membrane protein target expressed in multiple cancers, including ovarian and endometrial tumors, that is absent from or expressed at very low levels in healthy adult tissues. CLDN6 is also expressed in lung, gastric, and testicular cancers, which broadens the therapeutic use potential.

COLLABORATION IS KEY TO SOLVING THE ISSUE

To attain our mission, Context has partnered with leading pharmaceutical companies and academic institutions to advance our programs forward, which Context has attempted to do in an

FIGURE 1



How hormones drive cancer initiation and recurrence.

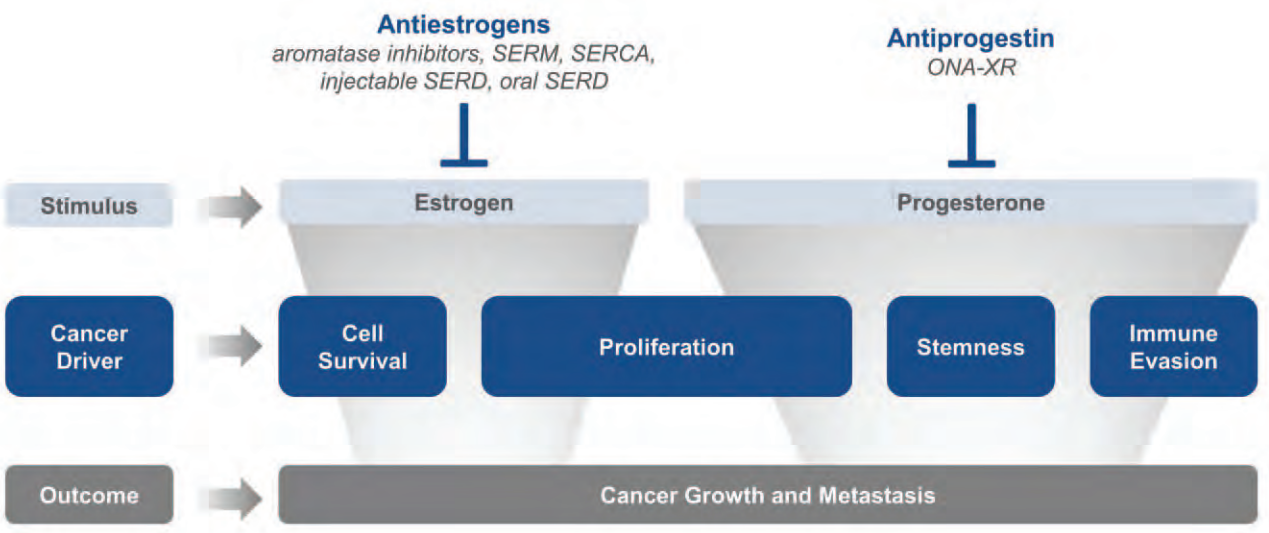
expeditious and cost-efficient manner. Context has outstanding pharmaceutical partners, including The Menarini Group (Menarini) and Integral Molecular (Integral). Through our partnership with Menarini, we are exploring the potential for complete hormone blockade in a Phase 1b/2 clinical proof-of-concept trial, referred to as the ELONA trial, by administering the combination of ONA-XR and elacestrant, Menarini's oral selective estrogen receptor degrader (SERD). Through our partnership with Integral, Context licensed the rights to Integral's CLDN6 monoclonal antibody (mAb), and we have subsequently, in collaboration with Integral, converted that mAb into CTIM-76, a CLDN6xCD3 bispecific antibody.

On the academic side, Context has established a network of Investigator-Sponsored Trials (ISTs) to broadly interrogate the therapeutic potential of ONA-XR across breast, ovarian, and endometrial cancer. Through ISTs, we have been able to execute more trials than we otherwise would have given the inherent capital and bandwidth constraints that define a startup company. By partnering with leading academic institutions and clinicians, we believe we can unlock the full potential of ONA-XR.

ONA-XR PROGRAM

Currently, there are no approved therapies that selectively target progesterone receptor positive (PR+) cancers. Context has chosen PR antagonism in breast cancer as our initial therapeutic focus due to the well-documented biology of PR signaling as a mechanism of resistance to antiestrogen therapy in patients with hormone-dependent breast cancer. Hormone-dependent breast cancer cells express ER and/or PR that allow the cells to grow in the presence of the hormones estrogen and/or progesterone. Published data by D'Assoro et al suggests that PR signaling is predominantly required for breast cancer cell renewal (i.e., stemness) and metastatic spread, whereas ER is predominantly required for breast cancer cell proliferation.[5] By combining antiprogestin and antiestrogen therapy, breast cancer cell growth, renewal, and spread can be mitigated. Based on these data, we believe ONA-XR, in combination with current standard-of-care antiestrogens, has the potential to significantly improve clinical

FIGURE 2



Blocking cancer growth by combining antiestrogen and antiprogestin therapy.

outcomes.

ONA-XR is currently being evaluated in three Phase 2 trials and one Phase 1b/2 trial in hormone-driven breast, ovarian, and endometrial cancers. These trials are intended to establish safety, pharmacokinetics, pharmacodynamics, and anti-tumor activity at the recommended Phase 2 dose of ONA-XR to guide potential advancement in Phase 3 development. The Phase 2 clinical trials of ONA-XR include second or third line (2L/3L) ER+, PR+, HER2- metastatic breast cancer (mBCa), PR+ recurrent granulosa cell tumor of the ovary, and PR+ recurrent endometrial cancer. Context reported preliminary data from all three Phase 2 trials in 2022.

To help inform which patients may be most suitable for treatment with ONA-XR, we are evaluating multiple biomarker assays, including tools to monitor activated PR and ctDNA changes, both of which are being utilized in our ongoing clinical trials and may be used for patient selection in future clinical trials.

Context announced encouraging ONA-XR data in preclinical studies evaluating ONA-XR combination therapy in mouse models of cancer and the role of ONA-XR as an immunomodulatory agent at the American Association for Cancer Research Annual Meeting 2022. The preclinical data for ONA-XR support it is a potent, specific PR antagonist. The data further highlights the breadth of ONA-XR's potential as a promising combination agent with standard-of-care therapies, as well as with emerging therapies for hormone-positive tumors, such as immune checkpoint inhibitors and inhibitors of the AURKA/STAT3 oncogenic axis. One particularly exciting piece of data presented came from Lauryn Werner, MD, PhD candidate, of the University of Kansas, wherein Dr. Werner showed that ONA-XR was able to induce complete tumor regression in syngeneic mouse models of breast cancer and tumor response was driven by the activation of cytotoxic T cells by ONA-XR in the tumor microenvironment. While ONA-XR was found to be highly active in mice with full immune systems, it was less effective in mice that were immunocompromised – thus, further underscoring the immunological activity of ONA-XR and why earlier studies of ONA-XR in immunocompromised mice may have missed the full potential of the agent as a therapeutic.

Context also reported data as of September 30, 2022, from an ongoing Phase 2 trial in collaboration with Jefferson Health investigating ONA-XR in combination with the antiestrogen anastrozole in women with PR+ endometrial adenocarcinoma who failed front-line therapy with a platinum/taxane-based chemotherapy regimen, the preliminary 4-month progression free survival (PFS) rate was 77.7%, based on nine evaluable patients. Further, 33% of patients were alive and progression-free at 12 months. This data compares favorably to the data from the KEYNOTE-775 Phase 3 trial where similar patients by treatment background were administered chemotherapy, which resulted in a median PFS of 3.8 months. Data also showed that only 4% of patients were alive and progression-free at 12 months after chemotherapy treatment.[6] There were no treatment-related serious

adverse events reported. The trial has enrolled 12 of 25 planned patients, three of which received treatment for greater than 12 months. Overall, seven patients remain in the trial. (ClinicalTrials.gov identifier:NCT04719273).

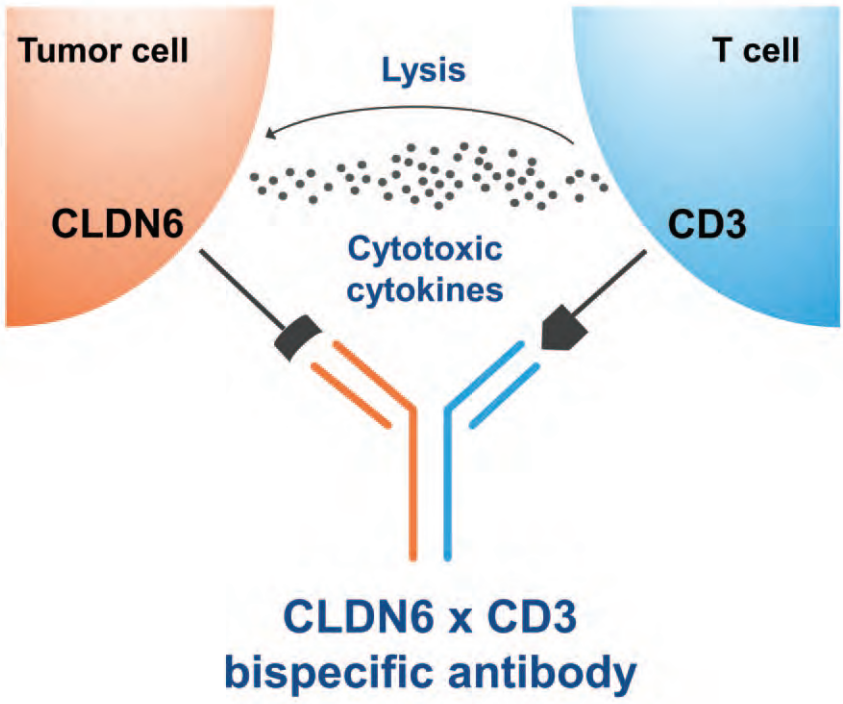
In collaboration with Memorial Sloan Kettering Cancer Center, an ongoing Phase 2 basket trial investigating ONA-XR 50mg BID as a single agent or in combination with anastrozole 1 mg QD in women with PR+ recurrent GCT of the ovary, Context reported data from two cohorts from the trial. In cohort 1, which treats patients with PR+ recurrent GCT with ONA-XR as a single agent, completed accrual to stage 1 and has shown a 12-month PFS rate of 20.1% and a Clinical Benefit Rate (stable disease) of 35.7%. Two patients continued on active treatment for greater than 18 months. One patient remains on trial in cohort 1. Cohort 4, which treats patients with PR+ recurrent GCT with ONA-XR in combination with anastrozole, enrolled 14 patients in stage 1 and will expand to stage 2 when greater than or equal to one response is observed. Seven patients remain on trial in cohort 4. There have been no treatment-related serious adverse events reported. (ClinicalTrials.gov identifier: NCT03909152).

At the 2022 San Antonio Breast Cancer Symposium®, data from the Phase 2 SMILE trial were presented. Being conducted in collaboration with the Wisconsin Oncology Network, the clinical trial is evaluating ONA-XR in combination with the antiestrogen fulvestrant in patients with ER+, HER2- advanced or mBCa who progressed on prior CDK4/6 inhibitor therapy. Preliminary Phase 2 findings highlighted a 4-month PFS rate of 44%, and favorable safety and tolerability. Context believes this initial data is encouraging based upon the EMERALD Phase 3 study in which fulvestrant monotherapy in a similar treatment population resulted in a median PFS of 2.0 months.

We are particularly excited about our partnership with Menarini established in August 2022. We entered into a Clinical Trial Collaboration and Supply Agreement with Menarini and initiated the Phase 1b/2 clinical proof-of-concept ELONA trial evaluating ONA-XR in combination with elacestrant in patients with ER+, PR+, HER2- mBCa who have previously been treated with a CDK4/6 inhibitor in November 2022. Context is sponsoring the clinical trial and Menarini is supplying elacestrant at no cost.

According to the American Cancer Society, breast cancer is the second most common cancer among women occurring in one in eight women (13%) over the course of her lifetime, with ~280,000 new cases of invasive breast cancer and 51,400 cases of non-invasive breast cancer expected in 2022. Elacestrant is the first oral SERD to demonstrate a statistically significant and clinically meaningful improvement in PFS versus standard-of-care (SOC) endocrine therapy in a Phase 3 trial in patients with ER+, HER2- mBCa, with 30% reduction in the risk of progression or death in all patients. Data also showed 22% of patients were alive and progression-free at 12 months after elacestrant treatment initiation versus 9% with SOC in the overall population.[7] Therefore, elacestrant may become the new backbone endocrine therapy for ER+, HER2- mBCa. However, emergence of resistance to elacestrant is a major therapeutic barrier to long-term clinical benefit. Context is exploring whether PR inhibition with ONA-XR in combination with elacestrant can reduce the emergence of resistance and further improve treatment benefit for patients with ER+, PR+, HER2- mBCa. Context anticipates Phase 1b data from the ELONA trial in the fourth quarter of 2023.

FIGURE 3



How Context Therapeutics' bispecific antibody works.

CLDN6 X CD3 PROGRAM

There is growing interest in applying antibody modalities, including bispecifics, antibody-drug conjugates, and CAR-T cell therapies to solid tumors. However, identifying appropriate tumor-specific targets that avoid adverse effects in healthy tissue has been challenging. The tight junction protein CLDN6 is a validated therapeutic target for many solid tumor types, including ovarian, endometrial, testicular, and gastric. It is differentially expressed on cancer cells with no reported expression in normal, healthy tissue. Despite being an attractive target, therapeutic monoclonal antibodies (MAbs) targeting CLDN6 are difficult to discover due to an abundance of closely related family members and an absolute need for high specificity. There are 27 human CLDN family members, and most are broadly expressed and highly conserved. The extracellular region of CLDN6 closely resembles the widely expressed CLDN9, which differs by only 3 amino acids. The few CLDN6 MAbs that have advanced to clinical development have all demonstrated significant binding to other CLDN family members, and most have now been halted from development. Using Integral's Membrane Protein Solutions antibody discovery platform, we have been able to isolate and optimize rare antibodies against CLDN6 that do not cross-react with other CLDN family members.

The specificity of our CLDN6 antibodies makes them amenable to use as the tumor-targeting arm of bispecific T-Cell Engagers. Starting with highly specific CLDN6 antibodies with a range of affinities, we engineered a large set (> 50) of CLDN6xCD3 bispecific antibodies (CLDN6 bispecifics) using multiple bispecific formats and CD3 arms that encompass different valencies and geometries. We designed the CLND6 arms to include antibody moieties with different affinities and stoichiometries, as these factors are expected to play a critical role in the potency of these molecules both in *in vitro* and *in vivo*. The full panel of bispecifics has been functionally tested in *in vitro* T cell cytotoxicity assays and has demonstrated potent killing of CLDN6-expressing cells with minimal killing of cells expressing other closely related Claudin family members. We have also extensively characterized this panel of bispecific antibodies for detailed binding to both CD3 and CLDN6, selectivity against closely related Claudin family members, and developability. The bispecifics were also screened for specificity against ~6,000 membrane proteins, representing > 95% of the entire human membrane proteome.

Solid tumors lead to 580,000 deaths annually in the US, and safe and effective therapeutics for many late-stage solid tumors are lacking. Ovarian cancer alone kills 14,000 people each year, according to the American Cancer Society, and many patients do not respond to currently available treatments. The specificity of our CLDN6xCD3 bispecifics suggests their potential to address the need for potent therapeutic modalities for CLDN6 positive ovarian and other cancers without compromising patient safety.

In November 2022, Context announced the selection of CTIM-76, a T cell-engaging bispecific antibody, as its lead clinical development candidate to target CLDN6 positive tumors. CTIM-76, is a CLDN6 x CD3 bispecific antibody that incorporates a highly selective CLDN6 binding arm and a CD3 binding single-chain Fv domain in an IgG format with a silenced Fc that is designed to be functionally monovalent to avoid aberrant T-cell activation and to enhance the safety profile. Research has demonstrated that CTIM-76 is potent with specific lysis of CLDN6+ cancer cells over normal cells and can activate cytotoxic T cells without concomitant activation of free cytokines – critical determinants of immunotherapy safety and activity. Preclinical studies suggest the potential for convenient dosing with low immunogenicity risk and manufacturing can be scalable to address the significant number of patients who are potentially eligible for CTIM-76 therapy. Context initiated Investigational New Drug Application (IND)-enabling studies and expects to submit an IND for CTIM-76 to the US FDA in the first quarter of 2024.

FUTURE & NEXT STEPS

Context believes it is growing in a pragmatic, stepwise fashion. Over time, Context aspires to become a fully integrated pharmaceutical company; however, it is our belief that being encumbered by large capital expenditure commitments, including research laboratories and commercial infrastructure, is currently a poor use of investor capital. Instead, Context retains a small footprint focusing on late preclinical through Phase 2 development. Pipeline assets have been externally sourced and development subsequently advanced through collaborations with other parties, including clinical research organizations and academic research centers. As the assets mature to commercialization, Context will consider whether to partner with large pharmaceuticals that have existing commercialcommercial infrastructures as a means to potentially enable Context to achieve economies of

scale and a flexible cost model to navigate the ups and downs of drug development.

Context's mission is to become a leading company in the women's oncology space, to prolong the lives of women living with these devastating cancers, and to provide women with a high quality of life while on treatment. To realize this mission, Context is advancing a pipeline of innovative products designed to address treatment resistance in breast, ovarian, and endometrial cancer, which, if approved, could provide patients with a much-needed new treatment options. ◆

This article contains forward-looking statements (FLS), which involve risks and uncertainties and do not guarantee future performance, as actual results or developments may be substantially different. Further information concerning risks and uncertainties associated with these FLS and Context's business can be found in our public disclosures with the SEC on EDGAR (www.sec.gov).

BIOGRAPHY

Martin Lehr is the Co-founder and CEO of Context Therapeutics. In addition, Mr. Lehr serves on the Boards of Praesidia Biologics and CureDuchenne Ventures. Previously, he was part of the founding team at Osage University Partners, a venture capital fund focused on academic spinouts from leading research institutions. Prior to Osage, he conducted research at the Sloan Kettering Institute in DNA repair and at the Children's Hospital of Philadelphia in thrombosis and hemostasis. He is a Director of BioBreak, a biotech executive peer networking group with over 2,500 active members across the US, and an Advisory Board Member of Life Science Cares and Life Science Leader magazines. Mr. Lehr earned his MA in Biotechnology from Columbia University and his BA in Economics from the University of Pennsylvania.

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CLINICAL TRIALS

The Mission to Increase Diverse Clinical Trial Participation

By: Lauren Chazal, MBA, and Keidra Gaston, MBA

Clinical trials are critical to advancing medical knowledge and new therapeutics. It is important that participants in clinical trials represent their entire communities and the potential recipients of new treatments. If participants are not diverse, clinical trials may not be able to accurately evaluate how well new treatments will work in underrepresented groups. In a study of more than 20,000 trials representing approximately 4.7 million participants, researchers found that only 43% of the trials reported data on race or ethnicity.[1] Without accurate reporting of race and ethnicity data, there is no way to ensure clinical research centers are achieving trial enrollment that represents their communities.

Headlands Research is a leading international network of clinical trial sites. The company was established with the aim to significantly increase clinical trial participation, provide faster study start-up, improve patient retention, and exceed industry standards with high-quality data. Its network of exceptional sites across the United States and Canada gives the company a substantial footprint in the clinical research landscape and allows it to profoundly impact the trials process by focusing on diversity, quality, and cutting-edge technology.

"Headlands Research's goal is to enable the approval of high-quality therapeutics that will benefit all patients in need, with a particular focus on the inclusion of populations that are traditionally underserved in terms of ethnicity and geography," said Mark Blumling, CEO and Founder of Headlands Research.

Headlands Research aims to tackle systemic barriers that communities of color face when trying to access clinical trials by combining its network's experience in building sustainable, local clinical trial infrastructure with efforts that address lack of outreach, patient mistrust, and lack of available sites. Headlands' work has already begun with a new, groundbreaking partnership with a leading pharmaceutical company that will further advance Headlands Research's mission to improve diversity in clinical trials.[2] This partnership will launch new research sites in areas with highly diverse, medically underserved populations.

"Diversity is a key pillar of Headlands Research's commitment to ensure clinical trials represent broader populations," said Mark Blumling. "We are proud to partner with a leading pharmaceutical company as we take another meaningful step forward toward achieving this extremely important goal."

The importance of diversity in clinical trials cannot be understated. For reference, a Phase 2 trial of an Alzheimer's disease drug included 360 participants in 83 sites and six countries. Even with its large geographic footprint, the study featured 97.5% White patients and only 2.8% Hispanic patients. Hispanics are one-and-a-half times more likely to be diagnosed with Alzheimer's than White people.[3] The participants in this trial were not reflective of the population this drug would aim to treat. This problem is reported in multiple other studies. Black men and women make up 15% of cancer patients but are only 4%-6% of cancer trial participants.[4]

There are several examples of previous research studies, such as the Tuskegee Syphilis Study conducted in the early to mid-twentieth century, which did not protect the rights and welfare of participants and caused unnecessary harm and deception among minorities. Despite the creation of regulatory bodies, such as Institutional Review Boards, minorities are more likely to be skeptical of scientific research than non-Hispanic Whites.[1] That is why rebuilding trust in communities is a critical focus of Headlands Research.

The partnership's first site is located at Headlands Research's facility in Brownsville, the largest city in the Rio Grande Valley, which spans the southernmost tip of Texas. The Brownsville site

New research finds that more than half of clinical trials do not report race and ethnicity data. SDI Productions/Getty Images. "Only 43% of clinical trials report race and ethnicity — What can be done?," by Timothy Huzar, 21 April 2022. Medical News Today.

focuses on multi-therapeutic and general medicine studies and has extensive experience in COVID-19 trials. Headlands Research's alliance with its pharmaceutical company partner is a multi-year commitment to create multiple diversity-focused sites. The Brownsville site has already implemented health fairs that include free health screenings, lunches, and educational talks from leading health experts. They have also sponsored the annual health and wellness fair hosted by the Brownsville Chamber of Commerce, where they connected with members of the community and provided them with information on upcoming vaccine trials and their no-cost health screening services.

In the past, prioritizing diverse clinical trial enrollment and retention has been met with minimal success. Headlands Research intends to change the landscape of the clinical trial process and offer a much-needed plan to eliminate health disparities and inequities in underrepresented groups. With more than 5,000 completed studies, 25 plus therapeutic areas of expertise, and more than 210 years of site research since its establishment, Headlands Research has the experience and the tools necessary to be a leader on the mission to increase diverse clinical trial participation. ◆

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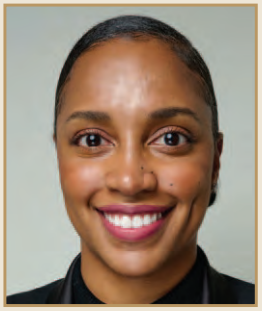
BIOGRAPHIES

Lauren Chazal is the Chief Business Development Officer for Headlands Research. She began her career in clinical trial operations with a privately held multi-site clinical research organization. Since 2012, she has held a pivotal role in business development and relationship management for clinical research sites globally. She graduated from Lehigh University with a dual degree in Finance and Marketing and from the University of Florida with an MBA.



Keidra Gaston is the Director of Marketing for Headlands Research. She began her career in business development for a hospital system and has held a lead role in marketing for a top healthcare insurance organization. She earned her MBA from Prairie View A&M University and her BA in Communication-Journalism from the University of Houston.

PATIENTS-ON-A-CHIP

Why Artificial Intelligence Will Be the Tipping Point to Remove the Faulty Reliance on Animal Testing in Drug Discovery

By: Dr. Isaac Bentwich, MD

INTRODUCTION

Advanced Bio-AI platforms that integrate artificial intelligence and machine learning with patients-on-a-chip, real-time nano-sensing, and stem cell genomic diversity technologies are the future of drug discovery and development.

The inability to predict which drugs will work safely in the human body has been a stumbling block since the advent of pharmacology. The reliance on inaccurate animal testing models to try to determine human efficacy creates massive time, cost, and safety challenges for drug development efforts. Animal testing is so ineffective in predicting clinical safety and efficacy that it is almost always wrong.

Industry leaders agree the current drug development process is flawed and are eager to help navigate the next era of pharmaceutical industry breakthroughs – using AI-powered patient-on-a-chip technology to improve predictions of clinical safety and reduce drug development cost while accelerating timelines. With regulatory changes to remove animal testing mandates underway, the path forward for AI-based technologies to disrupt decades of reliance on faulty testing models is becoming clearer.

FAULTY MODELS & HIGH FAILURE RATES

The inability to predict which drug candidates will work safely and efficaciously in the human body prior to expensive clinical trials continues to create massive challenges for drug development. On average, discovering and developing new drugs costs more than $2.6 billion over 12 to 15 years.[1,2] Worse yet, an

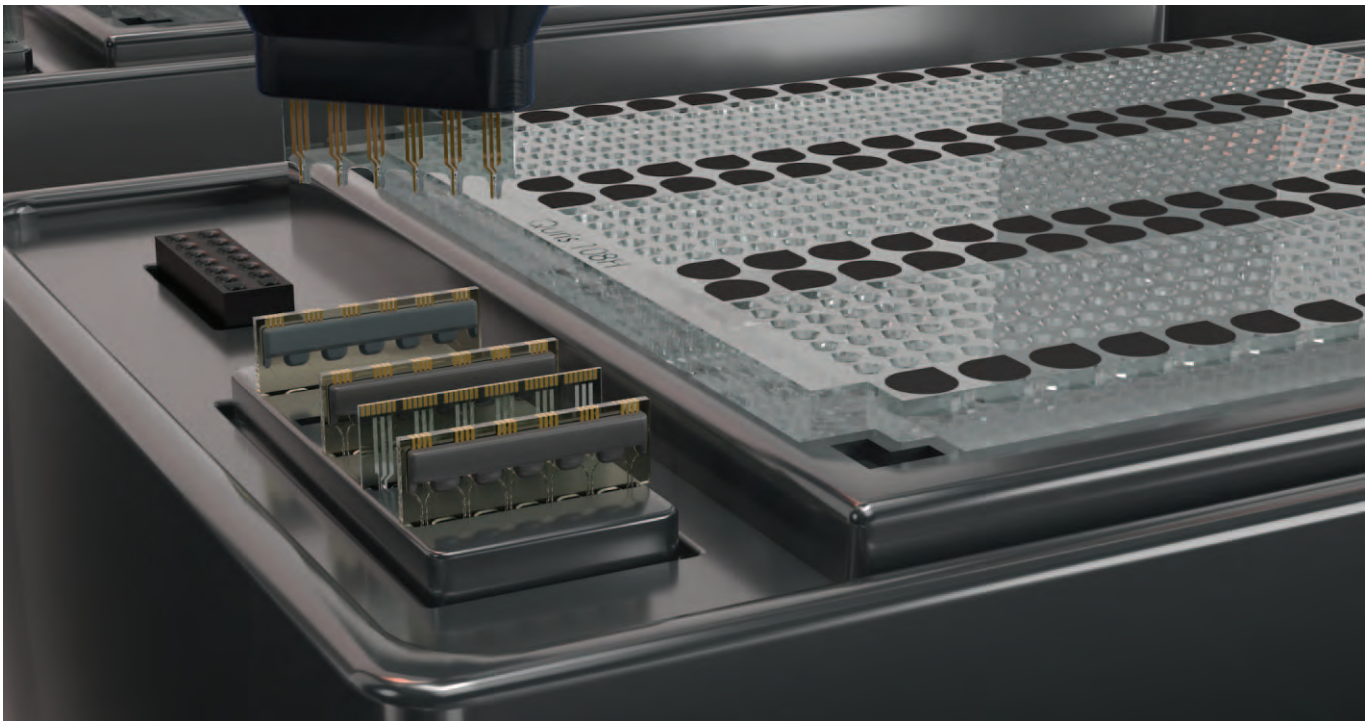
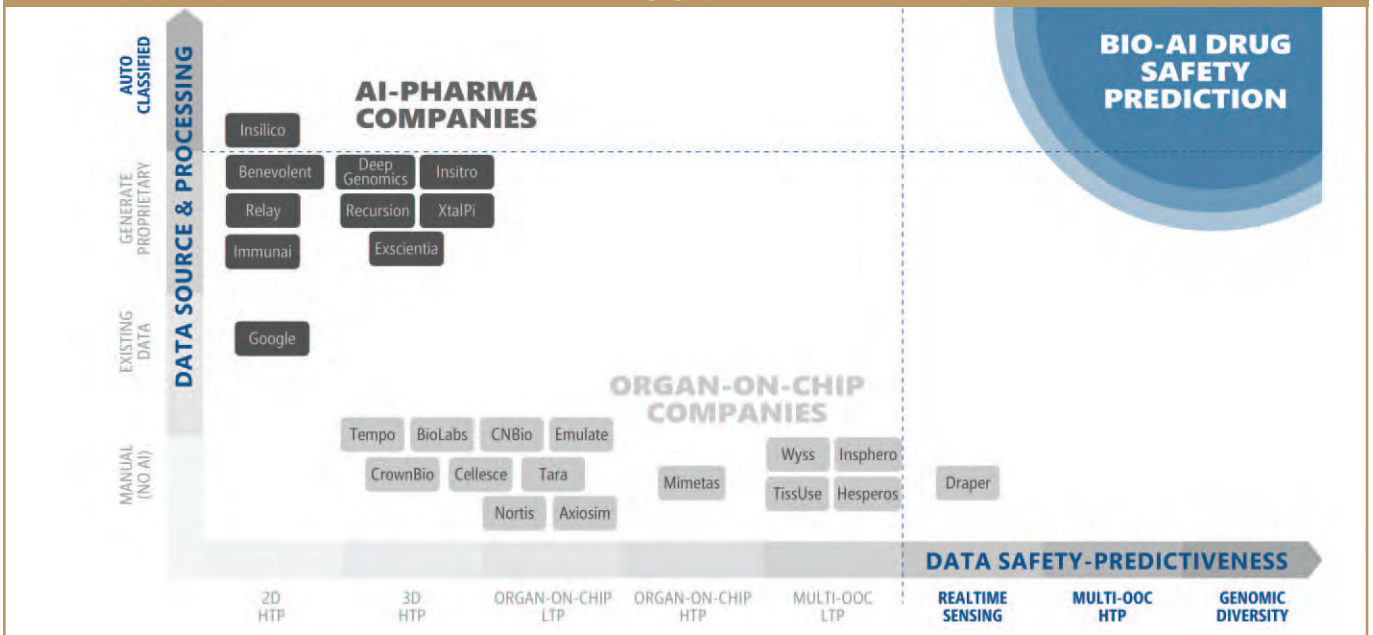


FIGURE 1



Machine Learning Versus Organ-on-Chip Approaches to Safety Prediction

analysis of the drug development cost structure found the average out-of-pocket success-cost to develop a drug currently averages $200 million, while the out-of-pocket failure-cost runs a staggering $1 billion.[3] In other words, for each successful drug developed, there is a massive, five-fold cost from failed attempts.

To date, animal testing models have served as the foundation for clinical prediction prior to clinical trials. Unfortunately, animal testing is an extremely poor predictor of clinical safety and efficacy. In fact, an astounding 89% of drug candidates that successfully pass animal testing fail in clinical trials.[4-6]

So why are clinical failure rates so astronomically high? According to Nobel Laureate Aaron Ciechanover, MD, DSc, "One of the main problems in drug development is the model that we are using – the mouse. We are not mice, so what works in animal-based trials is not a proper indicator of what will work for people."

Thankfully, awareness of the limitations of animal experimentation and the increasing pressure for alternatives has led to momentous regulatory developments. The FDA Modernization Act removes an 84-year-old statute mandating reliance on animal studies and replaces them with more modern, effective approaches.[7] In addition, the European Parliament recently passed a landmark resolution to phase out animal testing altogether.[7]

TECHNOLOGY BREAKTHROUGHS STILL MISS THE MARK

Artificial intelligence (AI) and machine learning (ML) approaches have accelerated and improved the drug discovery process by delivering qualitative, well-characterized drug candidates, but they still have not been able to solve the clinical prediction challenge.[8-10] While these companies have shown measurable savings and impact, most use ML to discover new targets, invent new molecules, find drug candidates that have better molecule-target fit, repurpose existing drugs, or improve our understanding of the mechanism of action of drug candidates to better anticipate and avoid off-target side-effects.

"Our drug discovery process is broken, and technology darlings across biotech, AI, ML, and big data have not been able to overcome the colossal clinical trial failure rate," added Dr. Kobi Richter, Founder and Chief Technology Officer of Medinol.

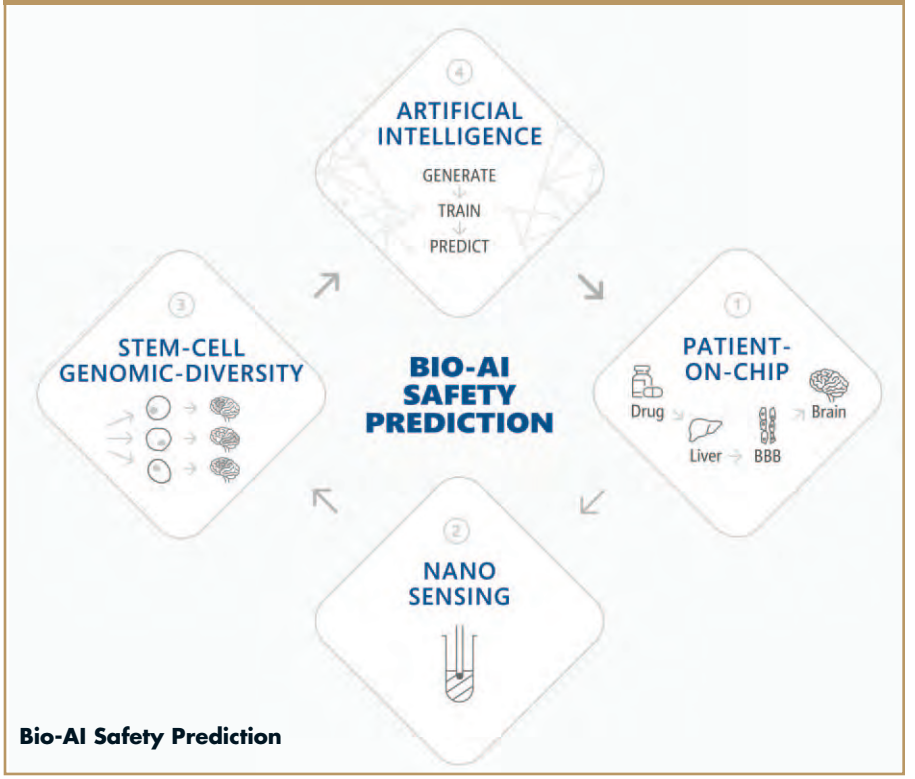
Existing ML platforms and organ-on-chip devices cannot offer reliable, high-throughput prediction for the clinical safety of drug candidates. Initially, AI-pharma companies relied primarily on existing data, whether it be publicly available data or data collected by other pharma and health organizations. Most AI-pharma companies today generate their own proprietary data, which they use to train the AI. However, current AI and ML models remain unable to determine if drug candidates are clinically safe and efficacious as each identified new molecule or target must still be tested to assess its actual effect in the human body.

Complicating matters further, not all biological data is created equal. Traditional organ-on-chip approaches that try to detect drug safety are modeled after antiquated animal studies: a single experiment that generates end-point data and is analyzed manually. AI that relies on traditional data points results in the same end point (mice-based trials) as previous (and woefully failing) drug development approaches, just faster. After traditional in vitro lab assays (including traditional 2D tissue cultures and other in vitro assays), they then still move into animal models, which are overwhelmingly (remember that 89% mentioned earlier) wrong when it comes to predicting if a drug candidate is safe and efficacious in the human body.

Luckily, there has been significant progress in the evolution of sophisticated 3D miniaturized organs – from the first organoid models 15 years ago, to organ-on-a-chip devices in the past decade, to robust validation as the technologies have matured in the past 2.5 years. However, miniaturized organ technologies face similar barriers as the AI/ML breakthroughs previously noted.

As the organ-on-a-chip field has evolved, its models have delivered higher levels of clinical predictiveness. Let's start with a quick look back at the evolution of organ-on-a-chip technologies. The first breakthrough, 2D models, poorly predict clinical safety – testing a molecule on a 2D model does not predict toxicity or pharmacokinetics and pharmacodynamics (PK/PD) in the human body.[7-9,11] Organoids, the most basic form of miniaturized organs or tissues, proved to offer better clinical predictiveness than 2D mono-cell, cell-line biology models.[1,7] However, organ-on-chip models added fluid replacement, mechanical ques such as microfluidic "shear-flow" and/or mechanical deformation, and, therefore, can offer much more sophisticated organ mimicking for specific organs. Organ-on-chip models have proven to offer better clinical predictiveness and data fidelity than organoid models.[6,7,12] A prime example, changes in stress-induced, elevated liver enzymes levels are absent in simple liver organoids but present in liver-on-chip devices in which the miniaturized liver is subjected to mechanical cues.[13,14]

FIGURE 2



Bio-AI Safety Prediction

However, despite continued advances, organoid and organ-on-chip devices are notoriously unscalable. Achieving intra-organoid variability remains elusive, and the expense and operational demands of multi-organ-on-chip technology puts it out of reach for mass research. Recent studies by the Wyss Institute used multiple interconnected organ-on-chips to demonstrate an unprecedented ability to discern drug toxicity and PK/PD, but each "patient-on-interconnected-chips" required a complex, expensive, cubic-foot size device – making it practically impossible to scale to run thousands of such experiments.[8,15] These devices are extremely expensive and require intensive manual labor by a skilled scientists – making it impossible to achieve the end goal of running thousands, and ultimately millions, of clinical prediction experiments reliably and inexpensively.

Currently, there is an enormous disconnect between AI and organ-on-a-chip modalities. While AI pharma companies rely on 2D biology, which is extremely poor predictor of drug safety, organ-on-chip devices ignore the power of AI/ML and rely mainly on manual data. While innovators continue to make significant strides in other stages of the drug discovery and development process – from determining a drug candidate's mechanism of action or identifying new drug targets, to designing new molecules and their validation – the clinical prediction challenge remains unsolved and has become recognized as a primary focus for the industry.

According to Prof. Robert Langer, Co-founder of Moderna and former Chair of the FDA's Science Board, "We are at the tipping point of the modernization of drug discovery. Predicting clinical safety is of huge value to pharmaceutical companies and the health of society at large."

PATIENTS-ON-A-CHIP – THE NEXT ERA OF DRUG DISCOVERY

The true tipping point will come from the seamless integration of maturing innovations, including AI, patient-on-a-chip models, stem-cell science, and nano-sensing. To effectively predict human efficacy and safety, we need a completely new path that combines advanced technologies into one platform and removes the current faulty, time-intensive reliance on mice from the equation.

Patient-on-a-chip models, also referred to as multi-organ-on-chip models, will play a central role. Patient-on-a-chip models are now being created in which multiple miniaturized organs are interconnected by a blood-like circulation system. These models have demonstrated superior recapitulation of drug systemic effect and unprecedented PK/PD assessment in synthetic in vitro systems.[2,6,8] Offering a remarkable breakthrough, Donald Ingberg's work at Wyss Institute demonstrated how interconnecting several miniaturized organs produces unprecedented, accurate predictions of PK/PD for several toxic drugs that were missed by animal model testing in some cases.[16] While this example linked multiple organ-chips with external pipes and pumps rather than relying on one, multi-organ chip, some systems are being developed with multiple organs on the same chip. But while multiple-interconnected-organs-on-chip systems offer a much higher level of data safety predictiveness, these systems were previously low-throughput and not easily scalable.[8,11]

Unlocking the full power of patient-on-a-chip technology requires an integrated approach. Other elements will be key to improving data safety predictiveness and accurately simulating a real human body reaction to drugs through patient-on-a-chip models, such as: real-time nano-sensing, high-throughput multi-OoC, and genomic diversity. Using next-generation, high-throughput patient-on-a-chip technology that leverages multiple, interconnected, miniaturized organs-on-a-chip to test thousands of known drugs, BioAI platforms can recapitulate their systemic effect and metabolism in the human body. As an example, each drug tested must first be metabolized by a miniaturized human liver, its metabolites then must interact with a miniaturized human blood-brain-barrier, and finally select chemicals would interact with a miniaturized human brain.

The platform must be able to run thousands, and ultimately millions, of experiments accurately and inexpensively. Miniaturization and advanced microfluidics will be key in addressing this challenge as making a significantly smaller scale patient-on-a-chip will reduce media volume, eliminate external pumps and tubes, reduce costs, and improve measurement sensitivity. Nano-sensing will also provide real-time measurements of metabolites and other biomarkers in the miniaturized tissues, creating time-series data for each of the metabolites monitored (such as oxygen, glucose, lactate) by documenting the response of various miniaturized organs to each administered drug. However, the nano-sensing measurements must be low-cost, highly sensitive, and create zero disturbance to accurately train the ML engine. Integrating nano-sensing technology with precision robotics and architecture miniaturization now make it possible to address these challenges – allowing high-throughput "dip-in" nano-sensing into the chamber housing the miniaturized organ to take multiple measurements over time without extracting any samples or affecting the concentration of metabolites in the well. Capturing microscopy images, such as fluorescent laser confocal microscopy, can monitor intracellular co-localization, in situ hybridization and changes in cellular morphology. Such nano-sensing capabilities increase the potential for more powerful organ-on-chip platforms, that harness real-time monitoring data, rather than relying on limited end-point data.

Stem-Cell Genomic Diversity to test known drugs on thousands of genomically diverse patients-on-a-chip creates a clinical-trial-on-a-chip by capturing the spectrum of diverse patient responses to a drug. Recent advances in stem cell automation technologies make this possible by rapidly creating hundreds of iPSCs relatively inexpensively from simple blood samples and then biologically programing each iPSC into different types of miniaturized organs (liver, brain, etc) on a chip.17 This allows the ML platform to learn not only to predict if a drug is generally safe, but also for whom is it safe – offering tremendous personalized-medicine ramifications in optimizing clinical trials, repurposing existing drugs and salvaging failed drugs.

When machine learning is at the center of an integrated Bio-AI prediction approach, it becomes fundamentally different from traditional biology and organ-on-chip approaches. The ML deter-

mines if a drug candidate will work safely in the human body. While patients-on-chip, nano-sensing, and stem cell genomic diversity all generate massive amounts of highly predictive drug safety data, the Bio-AI prediction approach does not rely on these components to directly detect the safety of a drug. Rather, the massive data they generate is used to train the ML, and based on that training, the ML can then predict drug safety – making it significantly different from traditional organ-on-chip approaches in both the data it uses and in how it uses this data. True Bio-AI platforms rely on thousands of experiments that generate massive, real-time time-series data, which is then used to train the ML. This approach harnesses the tremendous power of AI to predict drug safety.

Leading innovation in this field, Quris has developed a proprietary high-throughput patient-on-chip platform that integrates real-time nano-sensing to test thousands of known drugs, both safe and toxic, and then train the ML on the data generated, to better predict drug safety. With the scientific leadership of industry visionaries, including Nobel Laureate Prof. Aaron Ciechanover and Prof. Robert S. Langer, Quris has developed and proven a radically novel approach to drug development. The Quris BioAI platform (with 18 granted and pending patents) is the first AI clinical-prediction platform that simulates clinical trials and a real human body's reaction to drugs by leveraging a patented patient-on-chip system through the use of stem-cell-derived tissue and AI to effectively predict drug toxicity. Our exclusive collaboration with the New York Stem Cell Foundation, a world leader in stem-cell automation, will allow us to rapidly run experiments on miniaturized organs derived from hundreds of proprietary, genomically diverse stem-cell lines that train our Bio-AI platform to discern personalized drug safety.[17]

Technology advances have finally aligned to allow a massive transformation in drug development speed, safety, and cost. The next decade will bring an explosion of drug innovation as regulations and the industry take note. ◆

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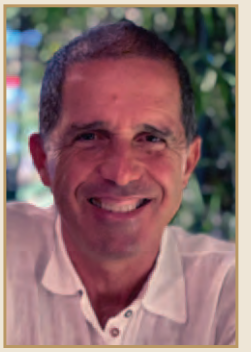
BIOGRAPHY



Dr. Isaac Bentwich is the Founder and CEO of Quris. Prior to Quris, he founded and led three bio-AI technology companies, each of which led revolutions in medicine, genomics, agriculture, and conservation. He is a physician and entrepreneur with a passion for leading interdisciplinary teams of scientists and technologists to tackle impactful challenges in the intersection between machine learning and life sciences; and to leverage and commercialize the resulting solutions. One of the companies he founded was Rosetta Genomics (NASDAQ:ROSG), which analyzed the human genome. He led the team at Rosetta Genomics in the discovery of hundreds of novel genes, more so than all the universities in the world combined, and delivered novel cancer diagnostics based on these genes. Its subsidiary, Rosetta Green (TASE:RSTG), was acquired by Monsanto for $35M. Under his leadership, team members at Rosetta went on to lead artificial intelligence at IBM, Google, and Microsoft. Now, at Quris, he and his team are using a similar bio-AI approach to disrupt the drug development process.

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Technology & Services
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Catalent's OneXpress® gives innovators integrated and tailored solutions that combine phase-appropriate scale and technologies with unparalleled manufacturing expertise across diverse dose forms, and an extensive supply network to deliver a successful product launch, faster. By taking a proactive approach and assessing production considerations early in development, Catalent's scientific teams help customers reduce their risk by working in parallel to address potential roadblocks and ensure robust processes from clinical development to launch. The OneXpress solution builds on Catalent's extensive expertise and integrated offerings in accelerating the scale-up of promising compounds into successful treatments, including OptiForm® Solution Suite and OptiForm® Total Supply. OneXpress requires only one transition point on the path from development to commercialization, removing the challenges and complexity of working with multiple providers. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

DIFFERENTIATED INJECTABLE DELIVERY

Credence MedSystems is an innovator in drug delivery devices. Credence's philosophy of *Innovation Without Change* results in products that impress and protect end-users while preserving pharma's existing processes, sourcing strategies and preferred primary package components. The Companion® family of syringe systems includes proprietary integrated needle-retraction technology, reuse prevention, critical safety & usability features as well as sustainability advantages. The Dual Chamber platform offers simplified delivery for drugs requiring reconstitution or sequential injection at the time of delivery. The Credence Connect™ Auto-Sensing Injection System incorporates automatic real-time monitoring of critical injection data into a reusable ergonomic finger grip. Credence's Metered Dosing product line allows precise delivery of small volumes and a force advantage when viscosities are high. For more information, call +1 844-263-3797 (+1-844-CMEDSYS), email info@credencemed.com, or visit **www.CredenceMed.com.**

TESTING SERVICES

DDL
Testing Experts. Service Specialists.

DDL is an independent third-party ISO 17025 accredited testing laboratory that provides packaging, device, and materials testing. For over 30 years, DDL has provided extraordinary service and specialized testing expertise to the medical device and pharmaceutical industries. We employ a team of engineers, technical, and quality experts devoted to helping our customers bring medical device and drug delivery products to market. Our single source, totally integrated approach enables organizations of all sizes from start-ups to globally recognized corporations maximize product performance, reliability, and safety while seamlessly achieving regulatory compliance. We work hard to build strong partnerships with our clients and have an unwavering commitment to assist in getting products to market on time. For more information, visit DDL at **www.DDLTesting.com.**

HANDS-ON FORMULATION SUPPORT

GATTEFOSSÉ

With application and R&D Centers in the United States, France, India, and China, the **Gattefossé** group is providing formulation support for oral, topical, transdermal, and other routes of administration. Equipped with state-of-the-art analytical and processing instruments, we stand to assist with your projects at all stages of development, from solubility screening to late-stage formulation and "proof-of-concept" studies. Moreover, we provide extensive regulatory support, sharing toxicological and safety data, and analytical/characterization methods. For more information, visit Gattefossé at **www.gattefosse.com.**

Technology & Services Showcase

On-Body Drug Delivery

SensAIR is a platform for on-body drug delivery that can deliver drugs of higher viscosity, such as monoclonal antibodies. The aim is to provide patients with the best possible support in the subcutaneous delivery of large-volume biologics. The ready-to-use SensAIR On-Body Delivery Device is easy to use and enables patients to start medication in a self-determined manner in familiar surroundings. The SensAIR On-Body Delivery Device can be adapted to medications of different viscosities and with different requirements. This applies to the size of the medical device as well as to the needle used, variable cartridge sizes and possible connectivity, for example to the patient's smartphone. Together with Gerresheimer's One-Stop-Shop quality promise, which includes a solution from the cartridge to the drug delivery device from a single source, SensAIR enables optimized delivery of biologics. For more information, visit Gerresheimer at **www.gerresheimer.com.**

Patient-Focused Delivery Devices

Nemera
we put patients first

As a world-leading drug delivery device solutions provider, **Nemera's** goal of putting patients first enables it to design and manufacture devices that maximize treatment efficacy. Nemera is a holistic partner and helps its customers succeed in the sprint to market with its combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open-minded, the company works with its customers as colleagues. Together, they go the extra mile to fulfil its mission. For more information, visit Nemera at **www.nemera.net.**

Injectable Drug Delivery

Owen Mumford
Pharmaceutical Services

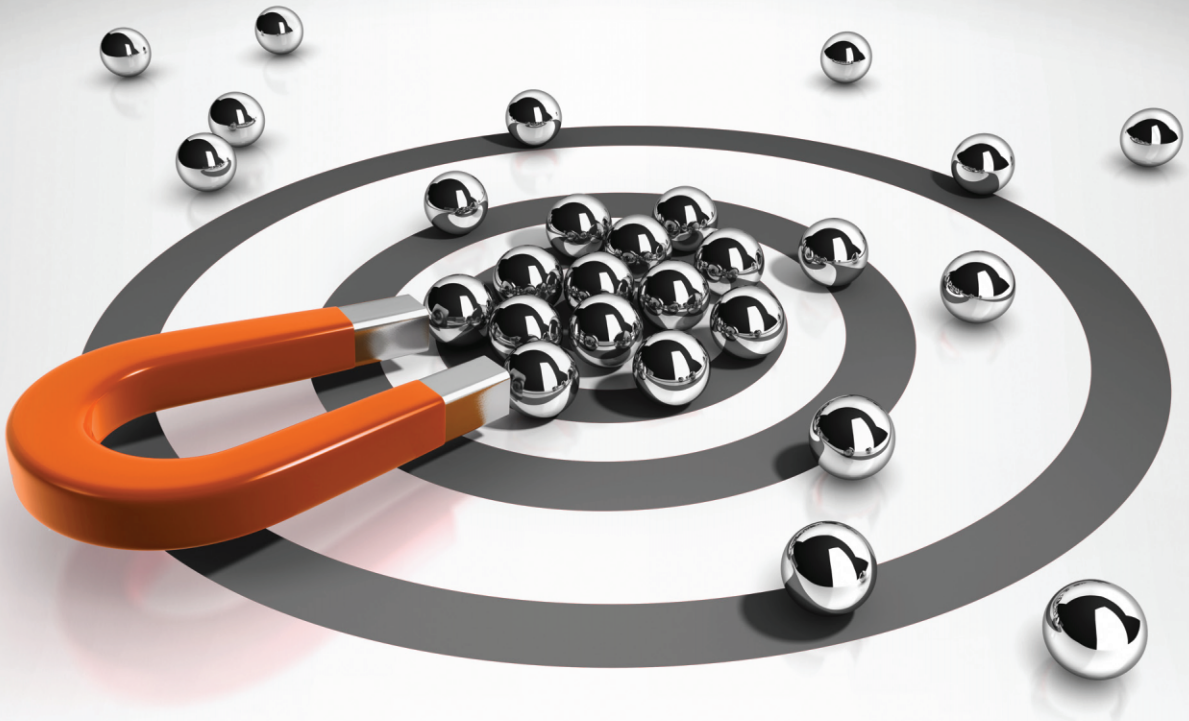
Owen Mumford Pharmaceutical is a specialist in the design, development, and manufacture of injectable drug delivery systems for the pharmaceutical, biotech, and generics industries. These include single-dose and multi-dose reusable and disposable auto-injectors, pens, and syringes for subcutaneous and intramuscular administration. Our innovative products are designed to meet both the need of our pharmaceutical partners and their patients by facilitating ease of use and improving safety and patient compliance. Our devices are also designed with the aim of reducing complexity and risk for the pharmaceutical and biotech industry in the development of their combination products. Our products are supported by our services, and we work with our partners every step of the way, supporting and guiding from initial concept stage through to taking the solution to market. For more information, visit Owen Mumford Pharmaceutical Services at **www.ompharmaservices.com.**

OINDP Development Services

proveris®
LABORATORIES

Proveris® Laboratories offers Orally-Inhaled and Nasal Drug Product Development (OINDP) expertise to pharmaceutical developers, including contract services employing new innovative *in vitro* techniques. These include measuring plume front velocity, evaporate rate, and quantifying deposition of inhaled drug products using human-realistic models. Employing in vitro approaches that are human-realistic can enable companies to make data-driven decisions and expedite product development and approval while saving time and resources. For more information, visit Proveris® Laboratories at **https://www.proveris.com/why-proveris/.**

SMART MARKETING
ATTRACTS THE RIGHT REACTION



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DEVELOPING NEW MEDICINES IS SCIENCE. SCALING UP A BIOTECH FOR A SUCCESSFUL LAUNCH IS ART.

The biotech journey from lab to patient has many challenges to navigate, all while accessing funding, building an organization, and moving your product through key development milestones. As an extension of your team, Catalent has the expertise you need from helping thousands of biotech partners successfully overcome and accelerate product development obstacles across stages, indications, and modalities.

Whether your objective is to advance to the next phase or partner throughout the full drug development process, Catalent's dedicated project management and deep scientific and technical teams, combined with the broadest range of technologies and flexible-scale manufacturing platforms, will help to steer your molecule toward the best chance at therapeutic and financial success. ***Let's partner on your next journey.***

Catalent® | *WHERE SCIENCE MEETS ART.*

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