Drug Development® & Delivery

April 2024 Vol 24 No 3

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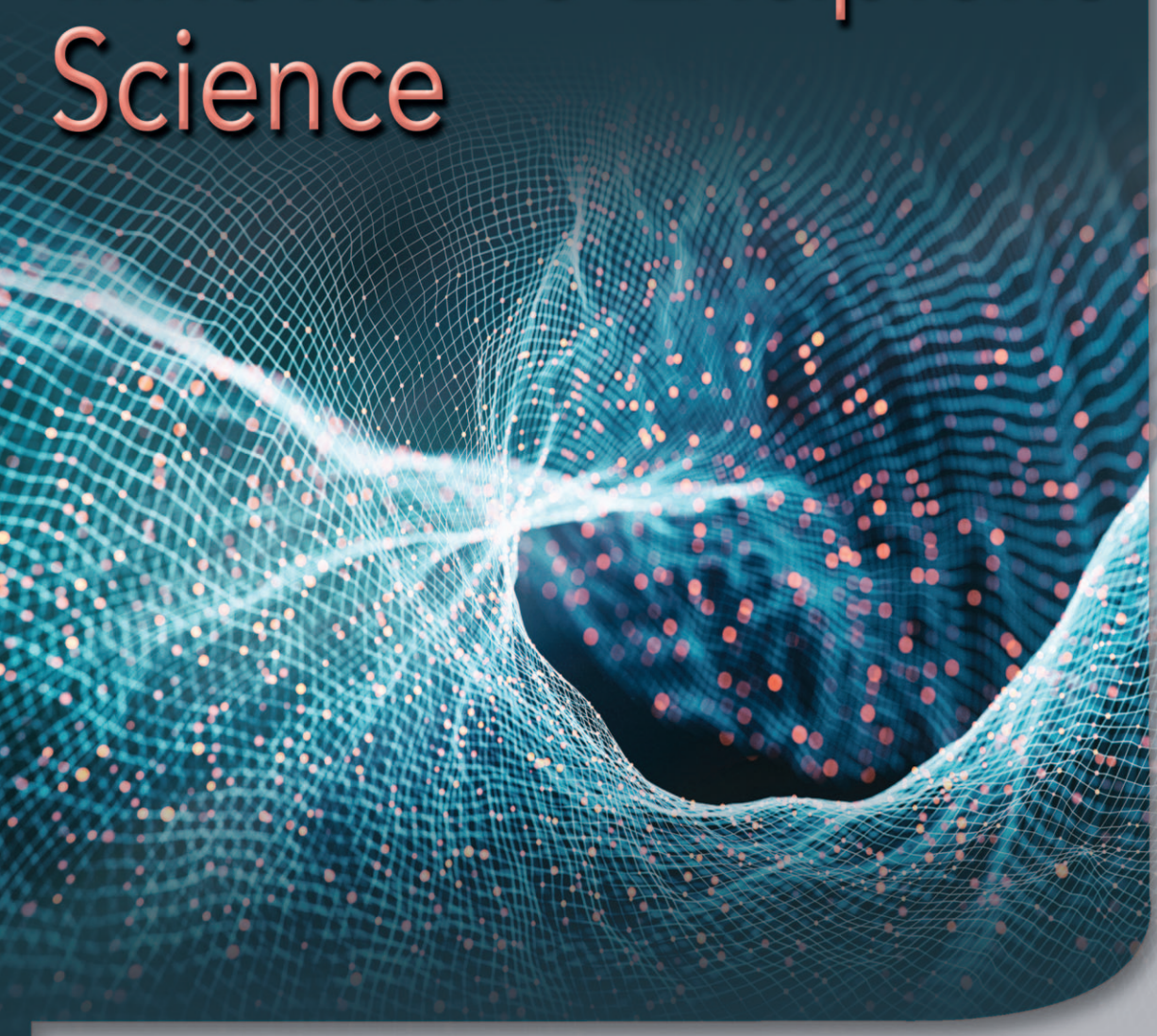
Innovative Excipient Science



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PETROS PHARMACEUTICALS' PRESIDENT & CCO

FADY BOCTOR

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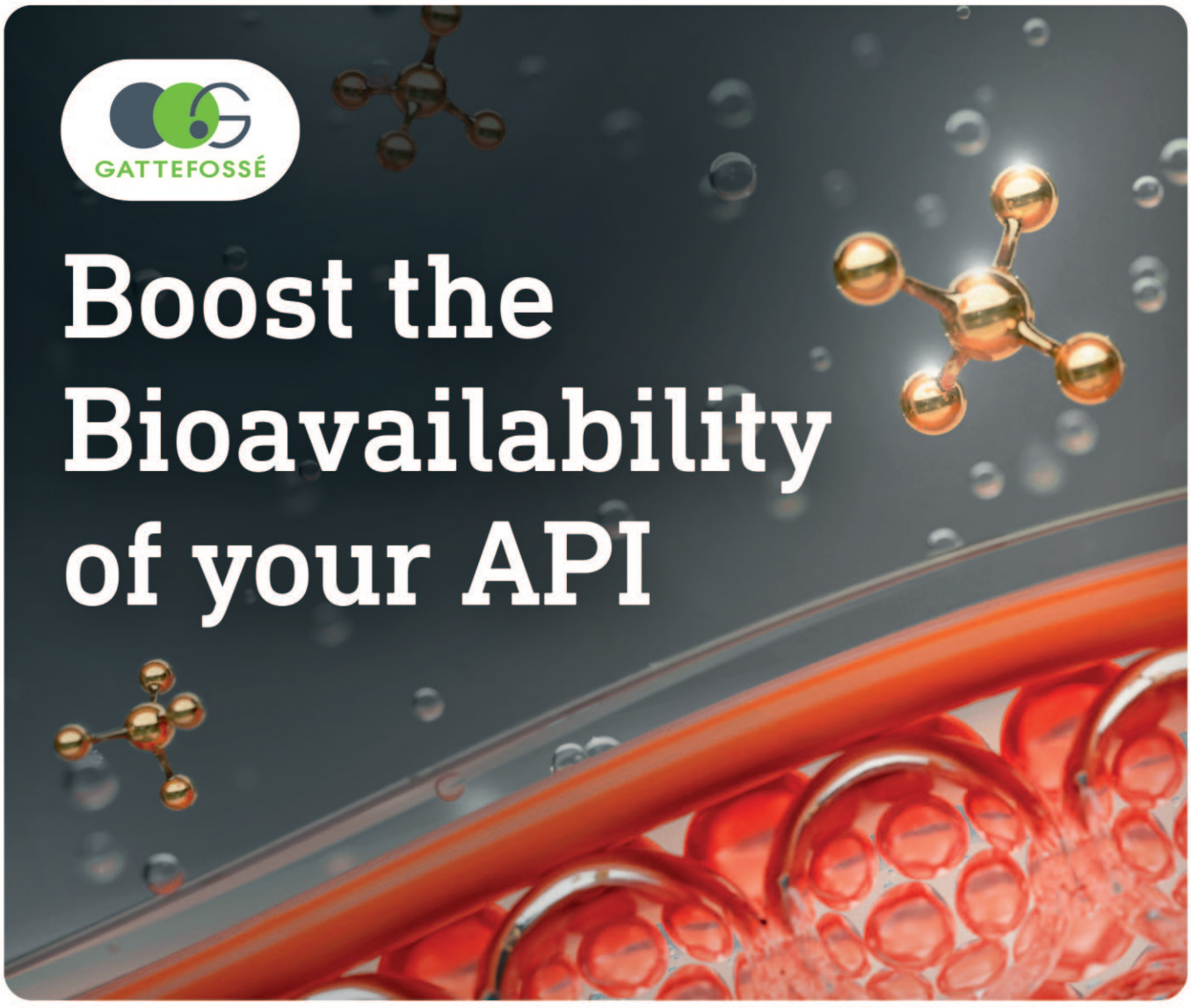

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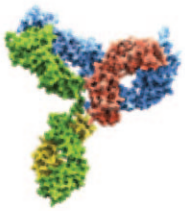
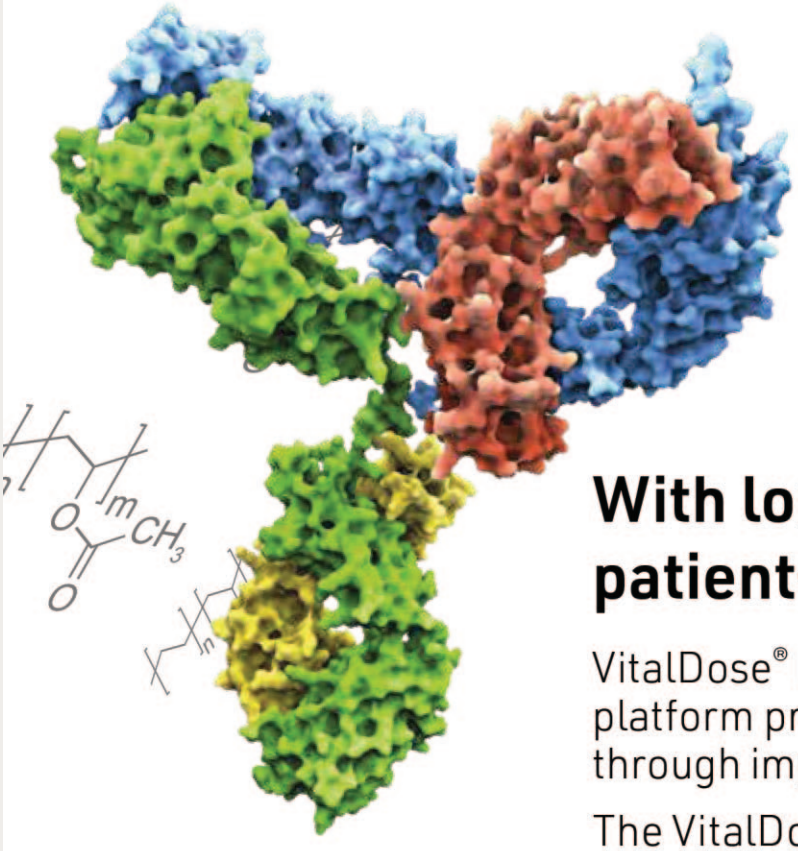
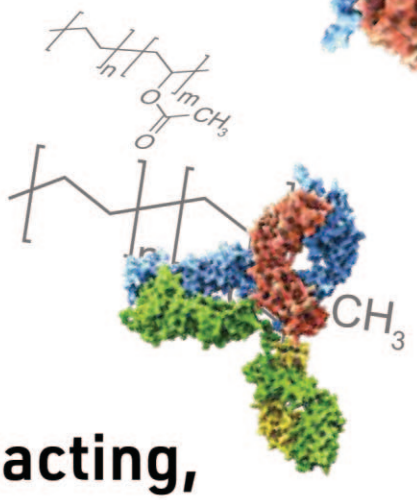
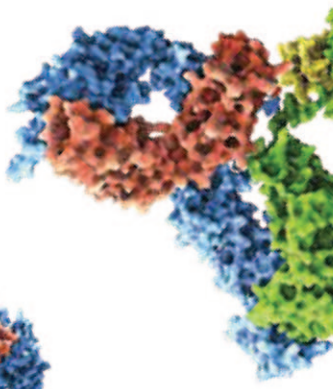


Sustained Drug Delivery







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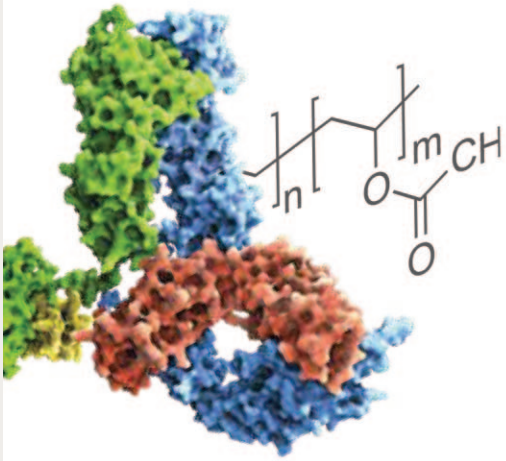

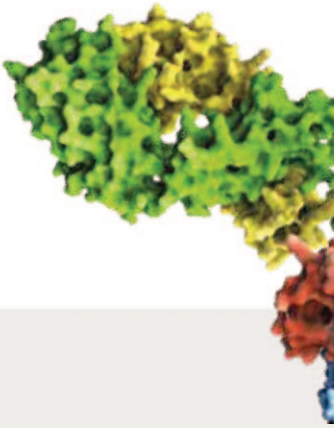

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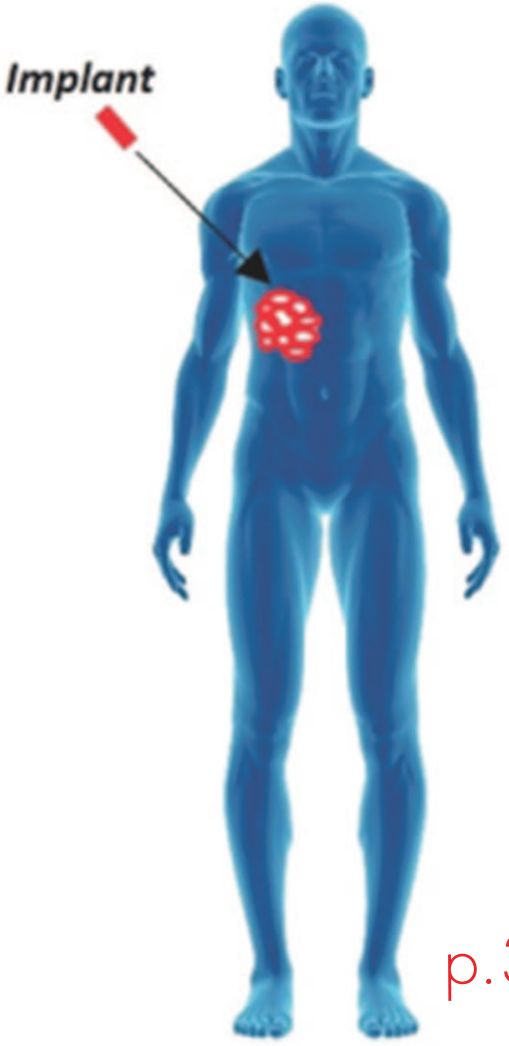
Website: Vitaldose.com

Drug Delivery Platform

"As the pharmaceutical development landscape continues to evolve, the search for effective drug delivery technologies continues to be a major driver of innovation. Traditional drug delivery methods, such as oral and injectable formulations, have long been the foundation of therapeutic treatment. However, these approaches have limitations when delivering peptides, biologics, and RNA therapeutics. Innovative drug delivery technologies can help improve drug efficacy, address toxicity issues, and improve patient compliance, which all have potential to improve treatment outcomes."



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Innovative Excipient Science

"The pharmaceutical excipients market was valued at $10 billion in 2023 and is expected to reach almost $14 billion by 2028. Major factors impacting demand are increased R&D investments in novel excipients and growing emphasis on patient-centric formulations. Additionally, superior generics and biosimilars are driving demand for novel excipients and drug delivery platforms, which enable differentiated products for chronic diseases, repurposed drugs for new routes of administration. Novel excipients can play a critical role in achieving challenging technical targets that are not possible with traditional excipients alone."

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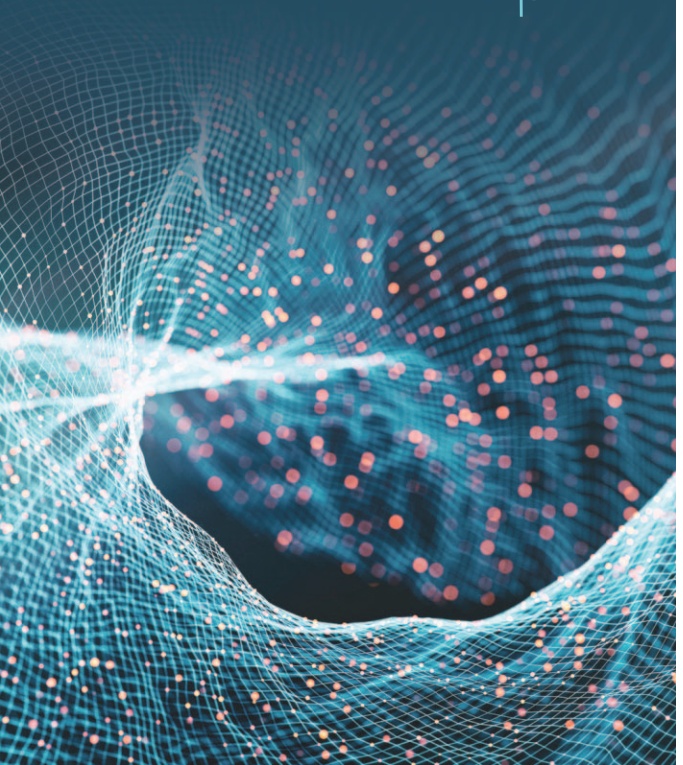

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e.g., Insufficient hardness, capping, insufficient API content uniformity

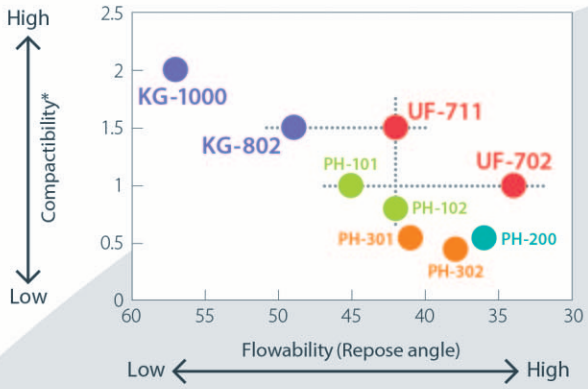
Enables unique and patient-friendly dosage forms
e.g., MUPS, multiple-API-combination tablets, small tablets

Improves the quality of formulations
e.g., Low nitrosamine-associated risk, less black particles, high-quality consistency

Grade lineup

Ceolus™ KG Highly compactible MCC with fibrous particles	KG-1000 KG-802
Ceolus™ UF Porous MCC with balance of compactibility and flowability	UF-702 UF-711
Ceolus™ PH Standard grade with high quality	PH-101, 102 PH-200 PH-301, 302

Map of Ceolus™ Compactibility vs. Flowability



* Comparison of tablet hardness, with the formulation of PH-101 = 1 set as the index point
Formulation: Acetaminophen/MCC = 70/30

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Pace Life Sciences Adds Liquid Capsule Filling Technology, Acquires New Jersey Laboratory From Curia

Pace® Life Sciences recently announced it has added liquid capsule filling technology to their comprehensive suite of oral solid dose development offerings.

"This new liquid capsule filling technology not only enables us to broaden our support from early phase to late phase clinical trials but increases our capabilities for viscous formulations and overlaying oxygen sensitive products with nitrogen," said Pace Site Head and Sr. Director, Lisa Z. Crandall.

The Lonza CFS 1200 Capsule Filling and Sealing Machine installed in the Pace cGMP manufacturing facility in Ann Arbor, MI, increases throughput of hard-shell liquid-filled capsules to a nominal speed of 1,200 per hour. This equipment can provide accurate filling, from 0.1 to 1.2 mL, into various sizes of capsules. Liquid formulations filled into hard shell capsules allow for delivery of poorly water-soluble drugs in pre-dissolved or self-emulsifying forms improving oral bioavailability.

Rob Tuohy, Vice President of Pharmaceutical Development, added "The addition of this technology completes our suite of services for supporting bioavailability enhancement of orally administered drugs. Between liquid capsule filling, spray drying, hot-melt extrusion, and nano-milling, we have all the tools necessary to enable our customers' drug development programs."

Pace Life Sciences, LLC, also announced it has acquired the Lebanon, NJ, laboratory facility (formerly Whitehouse Analytical Laboratories) from Curia, a global contract research, development, and manufacturing (CDMO) company. For more than a decade, this site has steadily cultivated partnerships across the biopharma industry through its ability to provide expertise and speed in development and commercial analytical laboratory services.

"This acquisition builds upon our leadership in the analytical services space to support emerging drug development partners through commercialization activities," said Eric Roman, CEO of Pace. "I am excited to leverage this expansion with the New Jersey team to further collaborate with our pharma and biopharma clients."

"Over the years, our Lebanon site has offered specialized analytical services that are highly valued by customers, and I am proud of the work that team has done," added Philip Macnabb, CEO of Curia. "However, these services fall outside of our core capabilities, and we determined that this site would be better served under the leadership of an owner with overlapping interests, while allowing us focus on our specialties – discovery, development and manufacturing of life-changing medicine."

The acquisition grows the Pace Life Sciences network to 9 sites able to support a wide spectrum of small and large molecule analytical services, formulation development, and early stage drug product manufacturing services. The New Jersey location allows the company to expand its capacity for FDA-registered central laboratory services, including analytical chemistry, microbiology, container closure integrity testing (CCIT), sterility, and other packaging and delivery testing services.

CAMP4 Therapeutics Announces Dosing of First Participant in Phase 1 Clinical Study for Potential First-in-Class Therapeutic for Urea Cycle Disorders

CAMP4 Therapeutics Corp. recently announced the first participant has been dosed in the company's Phase 1 clinical study of CMP-CPS-001, a potential first-in-class therapeutic for the treatment of urea cycle disorders (UCDs).

"This trial initiation is an exciting milestone, representing CAMP4's first investigational drug candidate to be studied in a clinical trial and one of the first mRNA-amplifying therapeutics in the clinic," said Josh Mandel-Brehm, CEO of CAMP4. "Most importantly, the clinical development of CMP-CPS-001 is a step toward potentially bringing a new, disease-modifying treatment to individuals living with UCDs. Going from initial screen to clinical initiation within three years provides further validation of the power and hyper-efficiency of our RAP Platform to create precisely targeted therapies for genetic diseases by amplifying mRNA to increase healthy gene expression."

UCDs are a group of rare, severe, inherited metabolic diseases impacting protein metabolism. People with urea cycle disorders accumulate excessive ammonia in their blood, which may cause irreversible brain damage, disability, and seizures, and may be fatal. These disorders occur across all age groups, from infants to adults, and mild symptoms may go unnoticed until a stressor — such as illness, protein consumption, or environmental stress — overwhelms compensatory functions, resulting in an acute metabolic crisis. No approved, disease-modifying therapeutics exist for the most prevalent forms of UCD, leaving patients, and their clinicians, with few tools other than nitrogen scavengers, strict diet, lifestyle constraints, and hyper-vigilant monitoring with supportive care during crises.

Mutations in genes encoding urea cycle enzymes result in insufficient levels of these important proteins. CMP-CPS-001 targets carbamoyl phosphate synthetase 1 (CPS1), a key enzyme that catalyzes the first step of the urea cycle. CMP-CPS-001 is designed to amplify CPS1 mRNA to potentially improve or restore urea cycle activity.

The Phase 1 study is a randomized, double-blind, and placebo-controlled study designed to evaluate the safety, tolerability, and pharmacokinetics of CMP-CPS-001 in healthy volunteers. The study is currently active in Australia and anticipates enrolling a total of 96 participants across single- and multiple-ascending dose cohorts. For more information about the Phase 1 clinical study of CMP-CPS-001, please visit clinicaltrials.gov (NCT06247670).

CMP-CPS-001 is an antisense oligonucleotide (ASO) designed to amplify CPS1 mRNA by harnessing fundamental cellular gene expression control mechanisms. CAMP4's proprietary RAP Platform enabled the discovery of CMP-CPS-001, a potential new therapeutic to treat urea cycle disorders.

CAMP4 is developing disease-modifying treatments for a broad range of genetic diseases where amplifying healthy protein may offer therapeutic benefits. Our approach amplifies mRNA by harnessing a fundamental mechanism of how genes are controlled. To amplify mRNA, our therapeutic ASO drug candidates target regulatory RNAs (regRNAs), which act locally on transcription factors and are the master regulators of gene expression. CAMP4's proprietary RAP Platform enables the mapping of regRNAs and design of optimal chemistry to generate potent therapeutic candidates to address hundreds of genetic diseases across multiple tissues.

Lonza Signs Agreement to Acquire Large-Scale Biologics Site in Vacaville (US) From Roche

Lonza recently announced it has signed an agreement to acquire the Genentech large-scale biologics manufacturing site in Vacaville, CA, from Roche for $1.2 billion.

The acquisition will significantly increase Lonza's large-scale biologics manufacturing capacity to meet demand for commercial mammalian contract manufacturing from customers with existing commercial products, and molecules currently on the path to commercialization within the Lonza network. The Vacaville (US) facility currently has a total bioreactor capacity of around 330,000 liters, making it one of the largest biologics manufacturing sites in the world by volume. Under the agreement, approximately 750 Genentech employees at the Vacaville (US) facility will be offered employment by Lonza.

Demand for capacity for commercial biologics is expected to remain high across the CDMO industry as innovative new therapies reach approval. In this context, the acquisition of the Vacaville (US) site will provide Lonza's customers with immediate access to significant new capacity in the United States, currently the world's largest pharmaceutical market. It will also create a significant West Coast commercial manufacturing presence, complementing Lonza's existing Biologics site on the East Coast, in Portsmouth (US), as well as its international network across Europe and Asia.

Lonza plans to invest approximately CHF 500 million in additional CAPEX to upgrade the Vacaville (US) facility and enhance capabilities to satisfy demand for the next generation of mammalian biologics therapies. The products currently manufactured at the site by Roche will be supplied by Lonza, with committed volumes over the medium term, phasing out over time as the site transitions to serve alternative customers.

Jean-Christophe Hyvert, President, Biologics, Lonza, said "The Vacaville site is a highly valuable strategic acquisition that will make capacity immediately available for our customers and unlock future growth for our Biologics division. It will support us in providing a commercialization path to existing customers and incremental large-scale commercial capacity to our partners. We have deep and long-standing industrial expertise in delivering commercial scale manufacturing services for our customers' therapies. In combining this with the strong legacy of the Vacaville facility, its highly skilled colleague community and its proven track record on quality, we are excited to take our leading large-scale mammalian offering to its next chapter of growth."

The transaction is expected to close in H2 2024, subject to customary closing conditions. Upon closing, the Vacaville (US) site will be integrated into Lonza's Biologics division, joining a network of existing mammalian manufacturing sites in Visp (CH), Slough (UK), Singapore (SG), Portsmouth (US) and Porriño (ES).

As the transaction is expected to be accretive to sales growth, Lonza has updated its Mid-Term Guidance 2024 – 2028. Its sales growth range was set at 11%-13% CAGR in CER, and has now been updated to 12%-15%. Mid-Term Guidance for CORE EBITDA margin and ROIC remains unchanged. The Mid-Term Guidance for the net debt/CORE EBITDA ratio and CAPEX trajectory also remain unchanged.

OKYO Pharma to Release New & Comprehensive Data GFrom Phase 2 Dry Eye Disease Trial

OKYO Pharma Limited recently announced it will be releasing new and comprehensive efficacy data readout from the Phase 2 trial of OK-101 in dry eye disease on March 22, 2024. The company will also host a Key Opinion Leader (KOL) event to discuss the findings in depth.

In a previous preliminary data readout, OK-101 showed statistically significant drug effects in FDA-recognized efficacy endpoints as early as the 15-day first visit after dosing. Additionally, statistically significant improvements were observed in both a "sign" (total conjunctival staining) and two "symptoms" (burning/stinging and blurred vision), which are FDA-recognized endpoints of dry eye disease.

The KOL call will feature prominent experts in the field of dry eye disease. The speakers will provide insights regarding the clinical significance of the OK-101 Phase 2 findings and discuss the potential implications for patient care and future research endeavors in DED.

"The upcoming data release follows the successful completion of OKYO Pharma's Phase 2 trial, which focused on assessing the efficacy and safety of OK-101, our novel topical therapeutic candidate for dry eye disease," said Gary S. Jacob, PhD, CEO of OKYO Pharma. "We plan to advance OK-101 into Phase 3 clinical trials in 2024, with the goal of developing a highly differentiated dry eye product to help patients underserved by current treatments. Our parallel development focus for OK-101 in 2024 is the evaluation of this drug candidate to treat neuropathic corneal pain for which we have already received IND clearance to begin clinical studies."

The double-masked, randomized, placebo-controlled Phase 2 trial was conducted at six sites in the US and enrolled 240 subjects with DED dosed twice-daily (BID). Patients were randomly divided into 3 cohorts, with one of the cohorts dosed with 0.05% OK-101 (n=81), a second with 0.1% OK-101 (n=80), and the third cohort with vehicle (n=79). The duration of a patient's treatment was 14 weeks, including a 2-week run-in period on placebo, to exclude placebo responders from the study, followed by 12 weeks in the randomized portion of the study.

OK-101 is a lipid conjugated chemerin peptide agonist of the ChemR23 G-protein coupled receptor which is typically found on immune cells of the eye responsible for the inflammatory response. OK-101 was developed using a membrane-anchored-peptide technology to produce a novel long-acting drug candidate for treating dry eye disease. OK-101 has been shown to produce anti-inflammatory and pain-reducing efficacy signals in mouse models of dry eye disease and corneal neuropathic pain (NCP), respectively, and is designed to combat washout through the inclusion of the lipid anchor built into the drug molecule to enhance the residence time of OK-101 within the ocular environment. OK-101 recently showed statistical significance in multiple endpoints in a recently completed Phase 2, multi-center, double-blind, placebo-controlled trial of OK-101 to treat DED.

ReciBioPharm & GeneVentiv Therapeutics Partner to Advance First AAV-Based Gene Therapy for Haemophilia Patients With Inhibitors

ReciBioPharm has recently announced a collaboration agreement with GeneVentiv Therapeutics to advance development of an Adeno-Associated Virus (AAV)-based universal gene therapy for haemophilia, and the first to treat haemophilia patients with inhibitors.

On average 30% of people with haemophilia A and about 5% of people with haemophilia B will develop an inhibitor (an antibody) to the treatment they receive to manage a bleeding episode. The ReciBioPharm and GeneVentiv partnership will help address the currently unmet need for AAV-based gene therapies for haemophilia patients with inhibitors.

GeneVentiv's GENV-HEM (AAV8.FVa) is the first, single infusion, universal AAV-based gene therapy for all types of haemophilia and has demonstrated therapeutic efficacy and safety in preclinical studies. This collaboration will see ReciBioPharm accelerate the development of this technology using its cutting-edge AAV manufacturing platform.

AAV therapy development is complex: the manufacturing process requires cost efficiencies, flexibility, and speed to be built into every stage of the process to ensure crucial milestones are met. ReciBioPharm will utilize its AAV platform at its Watertown facility in Massachusetts to advance GeneVentiv's therapy from early stage preclinical to Phase 1/2 clinical studies.

Xiaojun Liu, Director of AAV Process Development at ReciBioPharm, said "We are delighted to be working with GeneVentiv, an ambitious and innovative biotech who wanted to leverage not just our equipment and space, but our extensive knowledge and expertise too."

Damon Race, CEO of GeneVentiv Therapeutics, added "Gene therapies pose unique development and manufacturing challenges, so it was essential we chose the right partner to collaborate with, to minimize manufacturing risks and ensure we meet our key development milestones. ReciBioPharm quickly demonstrated that their team is the perfect development and manufacturing partner for our asset, enabling us to access their extensive experience and impressive capabilities. Our collaboration with them provides us with GLP and GMP product to meet both our IND and Phase 1/2 milestones."

Recipharm is a leading Contract Development and Manufacturing Organization (CDMO) in the pharmaceutical industry employing over 7,000 employees. Recipharm offers manufacturing services of pharmaceuticals and biologics in various dosage forms, production of clinical trial material and APIs, pharmaceutical product development and development and manufacturing of medical devices. Recipharm manufactures several hundred different products for customers ranging from big pharma to smaller research and development companies. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and is headquartered in Stockholm, Sweden.

GeneVentiv Therapeutics is a preclinical gene therapy company focused on blood disorders. Our lead program, GENV-HEM (AAV8.FVa), is the only single infusion, universal, AAV-based gene therapy able to treat all types of haemophilia. Unlike other AAV-based haemophilia gene therapies, GENV-HEM is the only gene therapy able to treat the 33% of haemophilia patients with neutralizing antibodies (inhibitors) to their missing clotting factor.

Sequel's twiist Automated Insulin Delivery System Receives FDA 510(k) Clearance

Sequel Med Tech, LLC recently announced its partner, DEKA Research & Development Corp., has received 510(k) clearance from the US FDA for the innovative twiist Automated Insulin Delivery (AID) system powered by Tidepool. The twiist AID system, which will be commercialized by Sequel Med Tech, LLC, is the first drug delivery system that directly measures the volume and flow of insulin delivered with every micro-dose. Cleared for people ages 6 and up with type 1 diabetes, the twiist AID system offers the capability and flexibility to address each patient's individual dosing needs.

AID systems integrate data from a continuous glucose monitoring (CGM) device, a control algorithm, and an insulin pump to automate insulin delivery, providing patients with the ability to manage their blood sugar levels more effectively. The twist AID system takes advantage of the FDA's medical device interoperability standards designed to help patients better tailor their treatments to their individual needs.

"The clearance of the twiist AID system is a pivotal first step in Sequel's quest to make day-to-day life easier for people with type 1 diabetes. The twiist system combines drug delivery technology that directly and precisely measures each dose of insulin, providing the opportunity for better control and flexibility," said Sequel CEO and Co-Founder, Alan Lotvin, MD. "Sequel is working to simplify living with diabetes by introducing product and process innovation while expanding access for all. It's why we expect to distribute twiist through the pharmacy channel so more people with type 1 diabetes have a convenient, affordable way to get started on an AID system. As we get closer to launch, we will share more details about additional initiatives designed to expand access and simplify the patient experience."

The twiist system incorporates FDA-cleared Tidepool Loop technology, which enables the system to automatically adjust insulin delivery based on CGM readings and predicted glucose levels. Sequel chose to partner with Tidepool, a diabetes-focused non-profit organization, because the underlying technology is community driven, designed for and by people living with diabetes, provides individuals with a high degree of customization and most importantly – delivers the clinical results patients are looking for.

"There's been a real need for continued innovation in insulin delivery, and the twiist AID system powered by Tidepool represents a substantial leap forward," said Howard Look, President and Chief Executive Officer of Tidepool. "The twiist AID system takes advantage of the Tidepool Loop algorithm, the first and only FDA-cleared glycemic controller that originated as a patient-led initiative. We are thrilled to see twiist come to market and bring new advancements to people living with type 1 diabetes."

The underlying drug delivery technology was developed by DEKA Research & Development Corp., birthplace of some of the most innovative and life-changing products of our time. DEKA was founded by Dean Kamen, an American inventor and entrepreneur who commercialized the first wearable insulin pump for diabetes, which he developed while still in high school. Kamen is a co-founder of Sequel and also created FIRST (For Inspiration and Recognition of Science and Technology) and FIRST Global, organizations dedicated to motivating the next generation to understand, use and enjoy science and technology.

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Purple Biotech Reports Preclinical Proof of Concept for its Tribody Platform Technology

Purple Biotech Ltd. recently reported preclinical proof of concept data for its conditionally activated tri-specific antibody platform.

"Our tribody platform is differentiated with its dual engagers including its NK cell engager having a dual mechanism of action, in addition to the conditionally activated T cell engager. We are excited about the potential of this platform to produce a pipeline of promising drug candidates that can be effective across numerous solid cancer tumors," said Gil Efron, Chief Executive Officer of Purple Biotech.

Prof. Amir Horowitz, Assistant Professor of Oncological Sciences, Precision Immunology Institute, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, added "Purple Biotech's tribody platform, apart from being a NK cell engager, via the anti-NKG2A arm, also functions as an important immune checkpoint inhibitor of both NK cells and specific subsets of T cells, unleashing both innate and adaptive immune systems against the tumor. This conditionally-activated platform requires a complex model for optimal and translational analysis, hence patient-derived explant (PDE) models were selected to demonstrate the added value of the anti-NKG2A modality."

Using 5T4-expressing lung cancer PDE model, where the immune cells and the tumor cells are derived from the same patient (autologous model), the studies showed a synergistic effect of the T cell engager and NK cell engager arms. While each bispecific agent, 5T4xCD3 or 5T4xNKG2A, showed only low response, the tribody platform's leading candidate IM1240 (5T4xCD3xNKG2A) having both engagers in one product, demonstrated a synergistic strong anti-tumor response. This effect is activated through the presence of 5T4 positive tumor cells. The advantage of the 5T4 arm was also validated using in-vitro PBMC-mediated cytotoxicity of cancer cell line studies which demonstrated 5T4-specific effect. While cytotoxicity at pM range was observed in 5T4-positive lung and breast cancer cells, no effect was observed against 5T4-negative cancer cells.

Purple Biotech's cleavable capping technology confines the compound's therapeutic activity to the local tumor micro environment (TME), which increases the anticipated therapeutic window in patients. This cap is attached to the anti-CD3 moiety and blocks its interaction with circulating CD3 positive T cells, thereby impeding potential off-tumor adverse reactions and also improving PK properties. The cap is designed to be cleaved off by multiple TME-specific proteases, which increase the likelihood for cleavage by many tumor types. Upon removal of this cap, the anti-CD3 moiety of the molecule is freed to bind and activate T lymphocytes against the tumor via CD3.

Purple Biotech Ltd. (NASDAQ/TASE: PPBT) is a clinical-stage company developing first-in-class therapies that seek to overcome tumor immune evasion and drug resistance. The company's oncology pipeline includes NT219, CM24 and IM1240. NT219 is a dual inhibitor, novel small molecule that simultaneously targets IRS1/2 and STAT3. A Phase 1 dose escalation study is being concluded and a phase 2 study of NT219 at its recommended Phase 2 level in combination with cetuximab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck cancer (SCCHN) is planned.

Bayer & Thermo Fisher Scientific Collaborate to Increase Patient Access to Precision Cancer Medicines

Bayer AG and Thermo Fisher Scientific Inc. recently announced they will develop next-generation sequencing (NGS)-based companion diagnostic assays (CDx) together. These will help identify patients who may benefit from Bayer's growing portfolio of precision cancer therapies by offering decentralized genomic testing and rapid turnaround time.

The CDx will be developed using Thermo Fisher's Oncomine Dx Express Test on the Ion Torrent Genexus Dx System, a fully integrated NGS platform that can deliver results on a patient's tumor or liquid biopsy sample in as little as 24 hours.

"We are committed to developing new treatment options for patients with unmet medical needs, reducing exposure to treatments that are not as likely to provide benefit or can spare them unnecessary side effects," said Christine Roth, Member of the Executive Committee of Bayer's Pharmaceuticals Division and Head of the Oncology Strategic Business Unit at Bayer. "The collaboration with Thermo Fisher Scientific perfectly complements Bayer's precision medicine strategy and fits our ambition to further advance the field of genomic testing and personalized treatment in Oncology, providing the right treatment to the right patient at the right time."

"We are committed to providing simple and fast next-generation sequencing-based solutions using tumor and liquid biopsy samples that support future access to targeted therapies, thereby helping to improve patient outcomes," added Garret Hampton, President of Clinical Next-Generation Sequencing and Oncology at Thermo Fisher Scientific. "The combination of our experience in developing distributable CDx tests with the game-changing turnaround time offered by our Genexus Dx System, allows clinical teams to quickly gather results to better understand the impact of these therapies. Pairing this with Bayer's growing precision oncology portfolio, we are well-positioned for the potential to help ensure that eligible patients can be quickly matched with the right treatment."

Thermo Fisher Scientific Inc. is the world leader in serving science, with annual revenue over $40 billion. Our Mission is to enable our customers to make the world healthier, cleaner and safer. Whether our customers are accelerating life sciences research, solving complex analytical challenges, increasing productivity in their laboratories, improving patient health through diagnostics or the development and manufacture of life-changing therapies, we are here to support them. Our global team delivers an unrivaled combination of innovative technologies, purchasing convenience and pharmaceutical services through our industry-leading brands, including Thermo Scientific, Applied Biosystems, Invitrogen, Fisher Scientific, Unity Lab Services, Patheon and PPD.

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FORMULATION DEVELOPMENT

Solving Tough Solubility Issues With Fewer Compromises & Better Outcomes

By: Anshul Gupte, PhD

INTRODUCTION

Approximately 40% of drugs with market approval and nearly 90% of active pharmaceutical ingredients (APIs) in the discovery pipeline have bioavailability challenges due to low solubility that can impact drug delivery.[1] In fact, bioavailability challenges result in new drugs under development either being delayed or failing to reach the market. To address this issue, there is now an array of enabling technologies available that help overcome the pharmacokinetic challenges of poorly soluble APIs.

There are two main causes of low solubility: high crystalline lattice energy and high lipophilicity. Because drug discovery continues to rely on high-throughput screening techniques to identify drug candidates based on receptor binding affinity, new chemical entity (NCE) pipelines are mostly composed of lipophilic compounds. Fortunately, enhanced solubility can be achieved using a variety of approaches. For oral solid dosage forms, well-established approaches include micronization, nanoparticles, amorphous solid dispersions (ASDs), lipid-based formulations, salts, and co-crystals.

MICRONIZATION: PRACTICAL PARTICLE SIZE REDUCTION

Particle size reduction technologies are routinely used to increase the bioavailability of poorly soluble drugs. The principle is relatively straightforward in practice: reducing particle size increases the relative surface area and, consequently, its rate of solvation. Because the degree of crystallinity is reduced, particularly at the nanoscale, apparent solubility increases, resulting in faster, more complete dissolution.

Although traditional milling and homogenization techniques are widely available for particle size reduction, these tend to be high-energy processes that may not be ideal for heat-sensitive APIs. However, alternative, lower-energy techniques are becoming increasingly widely used, using both top-down (cryo-milling) and bottom-up (nanocrystals) approaches. While bottom-up techniques typically result in smaller, more uniform particle size distributions compared with top-down methods, they require the API to have appreciable initial solubility, which limits their effectiveness with extremely insoluble compounds.

NANOCRYSTALS: SHAPING BETTER SOLUBILITY PROFILES

Nanocrystallization may help formulators deal with complex and poorly soluble APIs by offering better stability due to the crystalline characteristics of the particle. Nanocrystals improve solubility through an increase in the surface area beyond that

provided by micronization alone and can be administered as a dispersion in the liquid medium or the solid state. Amorphous nanoparticles offer even greater solubility enhancement, but they require mechanisms to maintain their stability in amorphous forms to prevent conversion to more stable crystalline forms.

Nanocrystals can be prepared by bead milling, high-pressure homogenization, and antisolvent precipitation. Another characteristic of nanocrystals that supports therapeutic performance is the fact that particles are 100% API and require no excipients. This technology can enable higher API drug loads per dose. However, this process requires surfactants as stabilizers, which may lead to new formulation complexities.

ASDS: IDEAL FOR HIGH-ENERGY APIS

ASDs offer better dissolution profiles and enhanced bioavailability by eliminating the crystal structure, making this technique ideal for APIs where high lattice energy is the main reason for low solubility. High lipophilicity can also be addressed by choosing a more hydrophobic carrier.

Both spray drying and hot melt extrusion (HME) can be used to produce ASDs. Several factors come into play including performance, projected dose, stability, and manufacturability. When determining which technology to employ for optimizing ASD's performance, two key factors should be considered: the physicochemical properties of the API and the phase of development, which influences the amount of API available for formulation development.

In the early stage of discovery, API availability is often limited, which makes spray drying the more efficient approach because the feasibility studies can be determined with much less API than with HME. For APIs that are amenable to HME, which is typically identified after proof-of-concept clinical studies, an initial spray-drying process can be converted to HME if necessary.

Important physicochemical properties for creating an ASD include the solubility of the API in a solvent suitable for spray drying, as it affects process efficiency, particle formation, API recovery, and formulation stability. HME is sometimes preferable as it does not rely on solvents. Notably, the heat and shear forces exerted during HME can be critical for overcoming tough solubility challenges but pose significant barriers when processing heat-sensitive APIs.

ASDs present several challenges to downstream formulation. Poor flow is one undesirable characteristic of spray-dried dispersions. Dry granulation can be employed to improve flow, but this technique can affect tablet compression. Due to the ratio of polymer to drug required to create stable ASDs, additional excipients are necessary to produce a reasonably sized finished drug product. Ideally, an increase in dose size is balanced by an increase in bioavailability, which allows for less-frequent dosing. Given the increased focus on patient centricity and compliance in today's drug delivery industry, size and swallowability are important considerations.

NOT TO BE OVERLOOKED: ASD PERFORMANCE *IN VIVO*

Residual crystallinity and re-crystallization of APIs during ASD processing also pose a challenge for drug development. Stability studies are required to ensure a viable product is developed. However, in vivo performance is often overlooked once the ASD has been optimized for its solid state.

ASDs are subject to what is often referred to as the "spring and parachute" effect. Compared with pure crystalline API, ASDs in the gastrointestinal (GI) tract exhibit more rapid and complete dissolution (the "spring") resulting in a metastable supersaturated solution of API. If this effect is not maintained or slowed by crystallization inhibitors, API precipitation can result, returning it to its most thermodynamically stable (ie, low-solubility) form. To prevent API precipitation and improve bioavailability, it is crucial to add polymers that act as a "parachute" effect, keeping the drug in solution after release into the GI tract and maintaining supersaturation. Although ASD polymers can provide additive effects, such as inhibiting crystallization or influencing the polymorph formed during recrystallization, their volume and the need for additional crystallization inhibitors should all be carefully evaluated to optimize in vivo performance and stability while fully capturing the benefits of ASDs.

LIPID-BASED DRUG DELIVERY SYSTEMS: AN EFFECTIVE ROUTE FOR THE RIGHT FORMULATION

Lipid-based drug delivery systems (LBDDS) are formulations containing a dissolved or suspended drug in a lipidic excipient. They can be filled into hard or soft gelatin capsules and provide an adaptable platform to deliver APIs that possess impediments to suitable bioavailability.

These formulations range in complexity from simple drugs in oils to doses designed to spontaneously emulsify upon contact with aqueous media – known as self-emulsifying drug delivery systems or self-microemulsifying drug delivery systems.

The versatility of this approach is a result of the number of excipients available to create formulations with targeted properties, including enhanced solubility and permeability, and sustained release. However, this variety, combined with how changes in composition affect solubilization, permeation, and stability can make the development of a LBDDS seem complex. Fortunately, CDMOs with lipid-based formulation development experience can offer extensive expertise that enables robust and expedited approaches for this development.

SALTS: OPEN WINDOWS TO SOLUBILITY BY CHANGING PH

One of the most frequently used approaches to increase the bioavailability of poorly soluble ionizable APIs is salt formation and salt selection. However, while particular salts and their formation can enhance solubility and the drug release rate, certain salt formation gets precipi-

tated and converted to its respective free acid/base form when it is orally administered, causing variability in exposure due to differences in solubility in the stomach and upper intestine. The location and extent of absorption are affected in vivo as the changing pH along the GI tract creates "windows" where more of the drug molecule is in its neutral form and can be more easily absorbed. In addition, the *in vivo* dissolution of some salts, especially hydrochloride salts, can be limited by the common ion effect of chloride in the GI tract. Overall, realizing the benefit of salt formation depends on the careful analysis of factors such as the API's inherent solubility, its acidity or basicity (expressed through pKa values), and the available options for salt formation to increase the chances of successful salt preparation.

CO-CRYSTALS: LOWER LATTICE ENERGY & HIGHER APPARENT SOLUBILITY

Unlike salt formation, co-crystal technology is best applied to non-ionizable APIs. A more contemporary approach to improving bioavailability, co-crystallization involves co-precipitation of an API with a soluble co-former, leveraging non-covalent intermolecular forces between the two compounds (primarily hydrogen bonds) to form a single-phase crystalline material with lower lattice energy and higher apparent solubility compared with pure crystalline API. The improvement in physicochemical properties, including solubility, dissolution rate, stability, and melting point, make co-crystallization a more attractive option for poorly soluble APIs. However, it is important to note that although co-crystals are more stable than ASDs, they suffer from the same "spring and parachute" effect, but without the additive effects of many ASD polymers on crystallization inhibition. Here, as well, additional formulation development is needed to optimize in vivo performance.

RESOLVING SOLUBILITY PROBLEMS REQUIRES SOLID ANALYTICS & PARTNERS

With so many viable options for bioavailability enhancement, developers who invest in thorough API characterization are well positioned to swiftly overcome challenges by identifying the technologies best suited to their drug.

However, the benefits of these innovations cannot be realized without a thorough characterization of solid-state chemistries. As new technologies and complex formulations enter the pipeline, careful development strategies and transparent partner collaborations will increasingly be seen as the best strategy to avoid delays in getting new therapies to markets and patients.

By working with specialist contract development and manufacturing organizations, pharmaceutical companies can access the expertise and infrastructure to overcome these challenges and harness new technologies. As a result, they can be confident they have the tools at their disposal to optimize the solubility, safety, and effectiveness of their formulations. ◆

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BIOGRAPHY

Dr. Anshul Gupte joined Catalent in 2022 and currently serves as Senior Director, Scientific and Technical Affairs. He has over 15 years of experience in product and analytical drug product development. He has contributed to several branded and generic regulatory submissions for US and worldwide markets. He has experience in working on drug product concept to commercialization from both a CDMO and sponsor prospective for a variety of solid oral and topical dosage form delivery systems. He earned his BPharm in India, his MS in Pharmaceutical Sciences from Temple University, and his PhD from the University of Kentucky. He also holds Regulatory Affairs Certification (RAC Drugs) from Regulatory Affairs Professional Society (RAPS).

THERAPEUTIC FOCUS

Perspectives on Sigma-2 Modulation as a Therapeutic Modality for Slowing Age-Related Degenerative Disease

By: Anthony Caggiano, MD, PhD

INTRODUCTION

The senior population in the US is expected to grow from 46 million today to 95 million by 2060.[1] This unprecedented growth is expected to fuel an increase in the number of elderly individuals requiring skilled nursing care for dementia, vision loss, and other conditions that can rob a person of their ability to live independently. Looking forward at the impending impact on the US healthcare system, we feel a distinct sense of urgency to find new treatments for age-related degenerative diseases, which may allow people to live independently longer.

A defining trait of many age-related degenerative diseases is the build-up of toxic proteins, oxidative stress, and inflammation. On a molecular level, these factors impair normal cellular function and ultimately lead to cell death. These cellular changes drive disease progression, translating to functional disability and loss of independence for people with Alzheimer's disease and other dementias, Parkinson's diseases, as well as neuro-ophthalmic disorders like dry age-related macular degeneration (dry AMD). Disease-modifying treatments for these and related conditions have eluded researchers – until recently.

Last year, we witnessed very positive news with the FDA approval of the first disease-modifying Alzheimer's disease treatment, LEQEMBI® (lecanemab-irmb injection for intravenous use) followed by FDA approval of the first complement inhibitor for dry AMD, SYFOVRE® (pegcetacoplan injection). The recent progress against these diseases reinforces our understanding of the factors driving disease progression and helps elucidate potential pharmaceutical targets, one of which is the sigma-2 receptor.

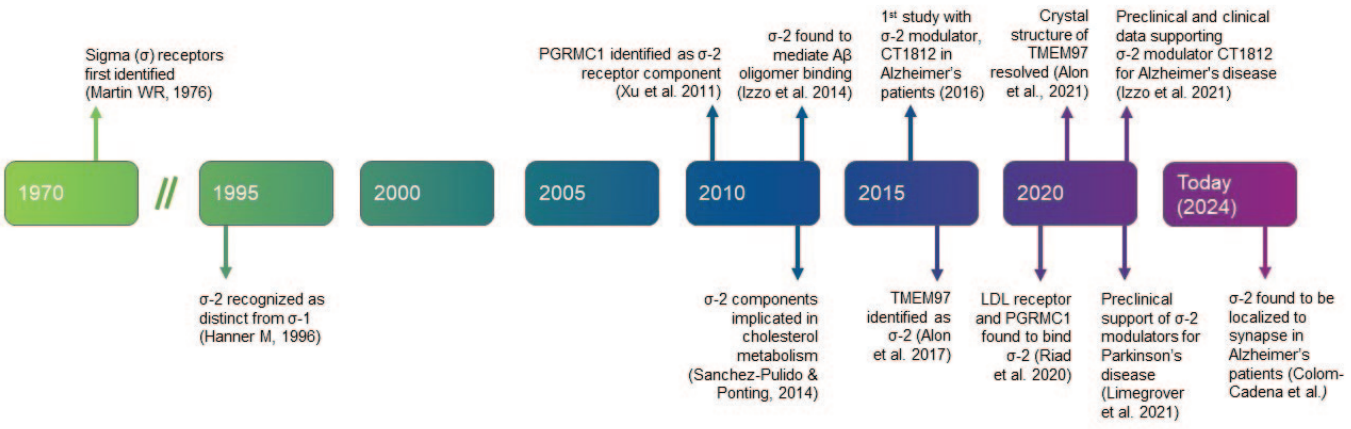
Cognition Therapeutics recently published a comprehensive review examining the sigma-2 receptor complex, which has been shown to have a role in Alzheimer's disease, dry AMD, and in synucleinopathies, such as dementia with Lewy bodies (DLB).[2] There is evidence the sigma-2 receptor acts as a regulator of cellular processes, such as autophagy and protein trafficking, which are impaired in age-related degenerative diseases. We have demonstrated in preclinical models these critical functions can be rescued by administering a sigma-2 receptor modulator, which we believe may protect neurons from the damage inflicted by protein aggregates, oxidative stress, and inflammation.

For these reasons, we and others believe sigma-2 represents a compelling drug target. Currently, Cognition Therapeutics is conducting Phase 2 clinical trials in adults with Alzheimer's disease, DLB, and geographic atrophy (GA) secondary to dry AMD with CT1812, an investigational, oral, small-molecule sigma-2 receptor modulator. CT1812 represents a distinctly new approach to targeting these degenerative diseases.

SIGMA-2 RECEPTOR MODULATORS IN DISEASE

Interest in sigma-2 receptors as therapeutic targets is growing given the high expression of these receptors in multiple cell types, including neurons in the brain and retina, which are susceptible to damage by pathogenic proteins, oxidative stress, and inflammation. The sigma-2 receptor has been shown to regulate cell functions disrupted by these toxins, such as cholesterol biosynthesis/trafficking, membrane trafficking, breaking down faulty proteins, lipid membrane-bound protein trafficking, and receptor stabilization at the cell surface.[2]

FIGURE 1



Timeline of the discovery and elucidation of sigma-2 receptor from inception to therapeutic modulation.[3-13]

In vitro studies provide experimental evidence that small molecule sigma-2 modulators can rescue these biological processes. Experimental sigma-2 receptor modulators tested by several independent research groups have been shown to be neuroprotective.

ALZHEIMER'S DISEASE

Synaptic loss is a hallmark of Alzheimer's disease and is characterized by a progressive reduction of synaptic density in disease-related brain regions.[14] The accumulation of Aβ is a hallmark of Alzheimer's disease progression and is believed to be a primary cause of synaptic dysfunction, dysregulation and eventually neuronal death.[15] Aggregated Aβ fibrils and plaque are now readily observable using PET imaging and are the targets of several approved and experimental immunotherapies.

However, while fibrils and plaques may be prevalent, Aβ oligomers are widely recognized as the most toxic. To date, their low molecular weight and relative scarcity has made them difficult to target with monoclonal antibodies. However, results from preclinical Alzheimer's models and from a small clinical study in adults with mild-to-moderate Alzheimer's disease show that oligomers can be displaced from synapses by targeting the sigma-2 receptor. In cultured neurons, this displacement facilitates synaptic recovery, which we expect will have a beneficial effect on cognitive decline.[6,16]

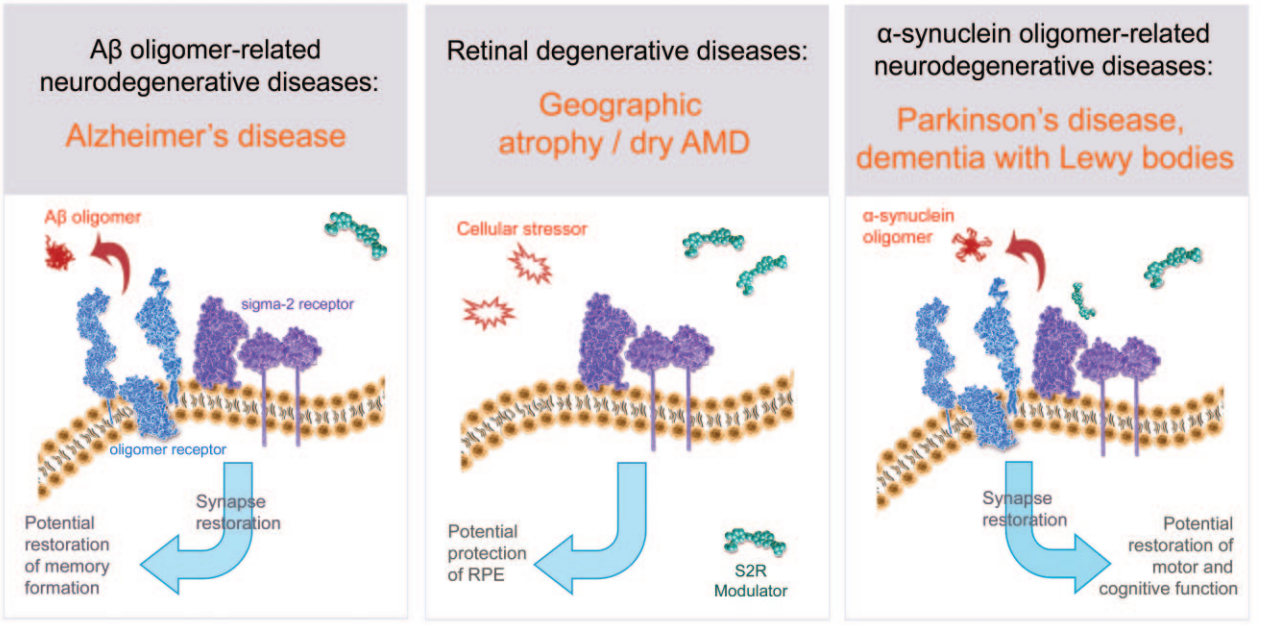
The clinical benefit of recently approved LEQEMBI, which targets soluble Aβ protofibrils, encourages the pursuit of therapies that target similar species of Aβ. There is potential for synergy between the sigma-2 receptor modulator, CT1812, which acts by displacing Aβ oligomers from synapses, and anti-Aβ antibody treatments that increase the clearance of these displaced Aβ oligomers. (Figure 2) Additionally, sigma-2 receptor modulators have been independently shown to rescue memory and cognitive deficits in an Alzheimer's mouse model, suggesting one of the major debilitating symptoms of Alzheimer's disease—the loss of ability to form new long-term memories—may be restored at a fundamental level by therapeutics targeting sigma-2 receptors.

ALPHA-SYNUCLEINOPATHIES: PARKINSON'S DISEASE & DEMENTIA WITH LEWY BODIES

Two primary alpha-synucleinopathies are Parkinson's disease and DLB, both of which are associated with motor function and cognitive decline due to synaptic dysfunction and loss.[17,18] There are currently no disease-modifying treatments for either condition. While the cell types and brain structures affected in Parkinson's disease and DLB differ, a common feature is the accumulation of alpha-synuclein aggregates, a major constituent of the Lewy bodies found in brain neurons. Increasing evidence suggests that alpha-synuclein also forms soluble oligomers, which are more toxic than fibrils.[19-21]

Based on our understanding of the role of sigma-2 receptors, we conducted preclinical research to determine the impact of alpha-synuclein oligomers on neurons with and without the addition of CT1812. As expected, we observed that alpha-synuclein oligomers are rapidly internalized into neurons, where they impair key cellular functions, such as protein trafficking and autophagy. The addition of the of sigma-2 modulator, CT1812, blocks the

FIGURE 2



Sigma-2 Receptor Targeting in Different Diseases of Aging
Structure-function of sigma-2 receptors and the role of small molecule modulators in restoring cell health and function. The Aβ oligomer receptor is a protein complex (light blue) that binds Aβ oligomers; small molecule modulator (green) binds to the sigma-2 receptor (purple).

internalization of alpha-synuclein, which reverses the trafficking disruption.[12]

DRY AGE-RELATED MACULAR DEGENERATION

Dry AMD, which affects approximately 2 million Americans, also involves a dysregulation of cellular processes including autophagy. When impaired, the retinal pigment epithelial (RPE) cells are unable to process debris generated by photoreceptors. As debris accumulates into deposits of lipid and protein, known as drusen, the architecture of the RPE is disrupted. Over time, damaged RPE cells die and are unable to support the photoreceptors, which leads to visual impairment.

Several lines of evidence suggest modulation of sigma-2 receptors may provide significant therapeutic utility for the treatment of dry AMD. First, several large-scale, independent genome-wide association studies identify a mutation in the gene encoding sigma-2 (TMEM-97) that confers decreased risk for dry AMD.[22,23] Second, proteomic analysis of cerebral spinal fluid (CSF) and plasma from the first cohort of a Phase 2 clinical trial of CT1812 in mild-to-moderate Alzheimer's disease (SHINE-A), showed the expression of many proteins known to be disrupted in dry AMD were altered by treatment with CT1812 versus placebo.[24] Lastly, *in vitro* studies showed the sigma-2 modulator, CT1812, rescued autophagy in cultured RPE cells that were put under disease-like conditions.[25]

Taken together, these data indicate CT1812 may slow disease progression and ultimately protect vision in people with dry AMD. The Phase 2 MAGNIFY study is currently testing CT1812 as treatment for people with dry AMD who have measurable geographic atrophy.

DEMANDING A RESPONSE

Alzheimer's disease, alpha-synucleinopathies, and dry AMD are important age-related degenerative diseases for which current therapeutics are unavailable, offer limited benefit, or require burdensome regimens. Yet the clinical and societal needs to address such diseases are profound. Alzheimer's disease prevalence is expected to more than double with related costs rising to an estimated $1 trillion by 2050 in the US.[26] According to the Parkinson's Foundation and the Lewy Body Dementia Association, direct healthcare costs for individuals with Parkinson's disease and DLB are estimated to be more than $55 billion combined. AMD is the leading cause of blindness in people over 50 years of age in the US and afflicts approximately 11 million people.

As we've previously discussed, the potential of sigma-2 receptor modulators to protect neurons in the CNS and retina and

by doing so preserve their function is compelling. The rigorous preclinical and clinical testing we have conducted, much of which is summarized in our published review, has given us the support we and regulators needed to advance CT1812 into Phase 2 clinical studies in adults with early as well as mild-to-moderate Alzheimer's disease, DLB, and dry AMD. While the specialty pharmacology trials we have completed have given us valuable insights into the potential of CT1812, the top-line results from the first of our Phase 2 studies, which we anticipate in 2024, will offer us the most concrete evidence yet of its therapeutic potential. If its activity is confirmed, CT1812 and other sigma-2 receptor modulators could represent a significant benefit for people with these devastating diseases and their families.◆

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BIOGRAPHY

Dr. Anthony O. Caggiano is the Chief Medical Officer and Head of R&D at Cognition Therapeutics. He has broad experience in the development of new medicines for neurological conditions having worked 17 years of at Acorda Therapeutics; he also served as CMO and head of R&D at Neurotrauma Sciences and earlier as acting President and CMO at Constant Pharmaceuticals and Aeromics, Inc. He earned his BA from the University of Virginia in interdisciplinary studies, focusing on biology, chemistry and psychology. He earned his PhD from the University of Chicago, and his MD from the University of Chicago, Pritzker School of Medicine.

ORGANIZATIONAL CULTURE

Assessing Quality Culture: Five Key Elements

By: Londa Ritchey, MBA

INTRODUCTION

There is sufficient passive endorsement of the idea that building and sustaining a strong quality culture is linked to enhanced business efficiency. Whether it is early detection and resolution of issues, or proactively avoiding the issues altogether, the results are not only an improvement in compliance, but also actual business efficiencies. So why hasn't a strong quality culture permeated the pharma Industry?

It takes some effort to define, improve, and quantify *Quality Culture*. Breaking down this term to try to define it seems to complicate the issue. Focus on the term Quality conjures thoughts of product/material testing or rote execution of compliance requirements. Focusing simply on the term Culture leads us to review behavioral aspects which, by nature, are qualitative and intangible. Neither of these terms, when taken separately, guide us to a better understanding of the target. Without formal definition and measurements, outlining the actions needed for improvement or monitoring is perceived as a non-productive use of business resources.

Let's start with a definition. Many describe *Organizational Culture* as how an organization behaves. Just like a community, each organization has known rules of engagement that include how to lead, communicate, interact, make decisions, reward, or recognize members and teach the next generation. *Quality Culture* within the pharma industry requires entrenching patient safety as the core foundation of the organizational culture. A strong *Quality Culture* is demonstrated through an everyday awareness, at all levels of the organization, of the impact our actions and decisions have on the ability of patients to safely consume the therapeutic products we make. The organization must incorporate consideration of patient and patient safety into all culture aspects of the business execution. There are five key priorities to consider when assessing the strength of your *Quality Culture*. This article explores these in detail.

MANAGEMENT OWNERSHIP OF QUALITY CULTURE

Management must set the tone and take ownership for a strong quality culture to endure. How management behaves, what is prioritized, and how team members are expected to engage with each other contributes significantly to the quality culture. Management influences these aspects everyday through their actions and both formal and informal communications. The entire organization is looking to the senior management team to understand what is expected within the organizational culture.

It is critical that all members of the C suite understand their influence and demonstrate their commitment to patient safety in everything they do. This does not usurp the importance of financials, strategy, technology, etc, however, failure to keep patient safety at the core of those critical activities goes directly against the mission statements of most companies to serve patients and to improve the quality of life of those patients.

Management is responsible for *Walking the Talk*, meaning management behavior should align with expectations the management team has for how the rest of the organization behaves. This is realized by in setting realistic goals and objectives that align with building and sustaining a strong quality culture. Goals should be based on resources available (or commitments to enhance resources) to accomplish those goals. Stretch goals can be

great for the company bottom line, but if these are impossible to accomplish with the current resources, then patient safety may be at risk.

Another important consideration is management visibility and empowerment of personnel directly responsible for daily operations decisions. Leaders should be aware of the complexity of the operations and understand the patient safety impact. This is aided by visits to the operations facilities and learning the processes in place.

Management must be approachable and open pathways for concerns to be communicated. When people feel empowered to speak up, the root causes of issues can be fixed promptly, and patient safety risks are avoided, or mitigated more quickly.

EMPOWERMENT & TEAM DYNAMICS

The decision-making authority for daily operations concerns related to patient safety impact also highlights the strength of the quality culture. If all decisions require escalation to senior management, how does that occur when management is not available? Will the tactical operators executing production be able to actively identify issues as they occur or are they likely to become passive since authority is with the management team only? Decision-making as it relates to patient safety, or raising concerns about patient safety, should be required, and enabled across all levels of the organization.

One way to identify a strong quality culture is to determine who is making the decisions when things don't go quite as planned. In a strong quality culture, everyone understands the risk to patient safety in everything they do and therefore can make the decision to stop the process if there is a perceived patient safety impact. It is also an environment where people are encouraged to speak up immediately when mistakes are made. Mistakes will happen in a production environment, and in an organization with a strong quality culture, mistakes are considered learning opportunities.

Rewarding the behaviors, or how things are accomplished, is key to ensuring the proper processes. All team members notice how others are managed when a non-conformance is noted. Is there a focus on removing the error traps to aid compliance or are operators and analysts expected to "do better"? In a strong quality culture, the operators and analysts associated with an error help identify contributing factors and are expected to aid in the implementation of the solution, based on their knowledge of everyday operations.

Team dynamics also factor into quality culture. Of course, team dynamics develop as a result of interpreting what is expected and rewarded within the work operations. Rewards and recognitions based on team successes drive a desire for team members to work together to accomplish a common goal. This does not mean that everyone contributes equally, but everyone should be expected to contribute to the best of their abilities. This requires a supervisor to monitor the dynamic and execution of the work. Everyone knows one bad seed can spoil the bunch. Those not contributing to the team outcome as expected need to be identified and managed quickly and properly to keep the rest of the team motivated.

QUALITY RISK MANAGEMENT

An immediate indicator of patient safety focus is the use of proactive versus reactive Quality Risk Management (QRM). The expectations provided in ICH Q9 (Quality Risk Management) and ICH Q10 (Pharmaceutical Quality System) guidelines are for product owners and manufacturers to proactively use QRM principles to identify patient safety risks. Marketing Authorization Holders and manufacturers will have the most detail about the product, production, and monitoring capabilities for specific products. This goes beyond complying with the formal regulations; this requires an in-depth knowledge of product and process, and using that to assess potential patient safety risks.

A sure sign of a poor quality culture is where a high volume of risk assessments are completed retrospectively in an attempt to justify something that is already done. This is particularly concerning when it is applied to the acceptability of a batch for release to the market. The perception is that the more a company invests in the production of a batch - and that can be very high costs of materials and components for biologics and gene therapies - the more you're biased to keep going or accept the batch because of the extreme costs (sometimes exceeding $1M). It is not always possible to avoid these retrospective risk assessments, especially in early phases when the process is still evolving. It is essential in those cases to preset the risk question, criteria for scoring risk, and acceptance criteria before starting the analysis. It is also helpful to utilize an independent facilitator for these assessments.

A mature QRM program is an effec-

TABLE 1

Positive Quality Culture Attributes	Meaningful Quality Culture Metric
Execution is Right First Time	RFT- Investigations, Batch Records, Testing, etc.
Minimizing time to complete issue assessment	TAT- Complaints, Investigations, etc.
On-time completion of commitments	% completed to Original Due Date: CAPA, Training, APR, PQR, QMRs, Audits
Minimal Repeat issues	Repeat Investigations, Complaints, Audits Issues

Example Positive Quality Metrics

tive indicator of a strong quality culture. It is achieved through the integration of risk identification and risk management within all areas of the quality system. There are several fundamental proactive risk assessments that should be in place to ensure patient safety. For example, contamination control and material/supplier quality risk assessments should be in place for all pharma manufacturing sites. Ultimately, the goal of quality risk management is to mitigate potential risks to the patient before these come to fruition. Conversely, retrospective risk management already has risk(s) posed and is dependent on unbiased decision-making to protect the patient. Therefore, minimizing the dependence on retrospective risk management is a more robust approach to protecting patient safety.

USE OF DATA & METRICS

Use of data and metrics can enable a strong quality culture. Pharmaceutical manufacturing produces an abundance of data. This can be overwhelming and distracting if there is not a strategy for collection and use of that data. Not all data has the same value. A strategy for data collection and monitoring should focus on the intended use of the data; what we hope to learn by using the data. For instance, will the data indicate that we are getting better or remaining within a state of control? Is the data collected in a meaningful way so that we can take actions based on the results? Is the data collected at a point that allows for preventative actions if trending in an adverse direction?

Part of the data strategy within a positive quality culture is the use of metrics. Defining metrics and setting metrics targets should prompt action. Metrics targets need to drive the right behavior, or at least avoid driving the wrong behavior. For example, the number of batches or activities completed within a given period should not be rewarded in a vacuum. Rather, the number of batches or activities completed right-first-time, with all proper controls and checks executed as expected, is what is best for patient safety. You don't have to be a statistician to know that it's possible to "play" with numbers to attain the acceptable result you want. This could mean not counting some events for a certain reason or including additional data to dilute an effect. It is important to define how data will be collected and calculated for each metric to ensure consistency and accuracy in assessing status of the quality systems.

Table 1 lists some suggested examples of setting metrics that aid in quality culture improvements.

KNOWLEDGE MANAGEMENT & CONTINUOUS LEARNING

Finally, we cannot underestimate the contribution of knowledge management and continuous learning opportunities to quality culture. Along with the data generated through production activities, there are new learnings with additional experiences with the product and process. Organizations with a strong quality culture maintain the practice of updating and sharing process and product knowledge in an efficient manner. There is ownership of the process knowledge and a responsibility for the owner to improve the monitoring and controls based on newly acquired information.

A continuous learning environment is one in which sharing of information is supported. Due to the complexity of operations within Bio/Pharma, mistakes will happen, and management should focus on rewarding the diligent identification and reporting of mistakes along with suggestions for potential solutions. To prevent repeat occurrences of the same errors, sharing these events as lessons learned is good practice. This includes setting specific time aside to review lessons learned on a consistent basis.

SUMMARY

Quality Culture requires a continuous focus on patient safety. This goes well beyond establishing a compliance culture

that abides by the regulations. A strong quality culture requires engagement from everyone from the operations floor to the C suite to understand the impact their role has on patient safety. It requires the establishment of processes that support both addressing known potential risks proactively and identifying new risks real time with an expectation of action. A continuous focus on patient safety requires a robust data collection and monitoring strategy.◆

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BIOGRAPHY

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VACCINE DEVELOPMENT

Therapeutic Vaccines Development: At the Edge of a New Revolution

By: Mario Davinelli, PhD; Narcisa Mesaros, MD; David Morland, BSc, CBiol; and Judith Neville, PhD

INTRODUCTION

The development of prophylactic vaccines is a fundamental aspect of modern medicine. In recent years, there has been a resurging interest in the creation of new vaccines, driven by a growing recognition of their importance in preventing infectious diseases morbidity and mortality and improving public health.

Recent advancements in vaccine development have opened new possibilities for the prevention of infectious diseases. These include the following:

- Adjuvants, which are molecules added to antigens with the aim to enhance the vaccine immune response.
- mRNA vaccines, a novel type of vaccine that use genetic instructions that direct the cells to make a protein antigen to induce a targeted immune response. This new vaccine platform proved its effectiveness in respiratory diseases prevention (e.g., SARS-CoV-2 and RSV).[1]
- Vector-based vaccines, which use a modified virus or bacterium to deliver antigens to the immune system, stimulating an immune response against the target pathogen. This vaccine platform proved its efficacy in preventing diseases like Ebola and COVID-19.

There has been a resurging interest in the development of new vaccines, driven by a growing recognition of their importance in preventing infectious diseases morbidity and mortality and improving public health.

THERAPEUTIC VACCINES

Therapeutic vaccines, known also as treatment vaccines, are a type of vaccine designed to treat or manage a disease rather than prevent it.

They work by stimulating the immune system[2] to recognize and attack specific cancer cells, infectious agents, or other antigens, and are used as a treatment strategy to cure or change the course of the disease.

Also, therapeutic vaccines differ from other types of immunotherapies, such as monoclonal antibodies, because they provide active immunization by therapeutically stimulating an immune response.

Immunotherapies based on passive immunization, on the other hand, transfer pre-synthesized elements of the immune system to the patient, so that the body does not need to produce those elements itself, providing short-term protection against infections or clinical conditions. Often, passive immunization is used when no vaccines are available and offers short-term protection, when the patient is immunocompromised or requires initial immune support.

Therapeutic vaccines can be used to treat cancer by targeting specific proteins or antigens that are present on cancer cells membranes. These vaccines can be designed to target a variety of cancers, including melanoma, breast cancer, and prostate cancer. The vaccines can be made from a patient's own tumor cells or from synthetic peptides that mimic the tumor's antigens.

Therapeutic vaccines for infectious diseases work similarly by stimulating the immune system to recognize and attack the infectious agent. These vaccines can treat chronic viral infections like HIV, hepatitis B, and hepatitis C.

Therapeutic vaccines for cancer offer a promising avenue for improving patient outcomes.

Therapeutic vaccines can be developed for autoimmune diseases as well, as they can be targeted against self-antigens involved in those chronic conditions.

One of the advantages of therapeutic vaccines is that they can be tailored to the individual patient's immune system. This personalized approach can improve their effectiveness and reduce the risk of side effects.

THERAPEUTIC VACCINES FOR CANCER

Therapeutic vaccines for cancer offer a promising avenue for improving patient outcomes.[3] They are designed to stimulate the immune system to recognize and attack cancer cells.

Therapeutic cancer vaccines employ various mechanisms to elicit an immune response against cancer cells.[4] Some common mechanisms include the following:

- **Antigen presentation:** Cancer cells often express unique antigens that distinguish them from the healthy cells. Therapeutic vaccines utilize these antigens to train the immune system to specifically recognize and target cancer cells.
- **Activation of immune cells:** Vaccines can stimulate the activation and proliferation of immune cells, essential for eliminating cancer cells (e.g., NKs).
- **Memory response:** Therapeutic vaccines aim to create an immune memory response: the immune system retains the ability to recognize and attack cancer cells, providing long-term protection against disease recurrence.

Therapeutic vaccines for cancer hold several potential benefits, including the following:

- **Targeted treatment:** Unlike traditional cancer treatments, they specifically target cancer cells, sparing healthy cells and tissues, therefore reducing the potential side effects.
- **Personalized approach:** Personalization to each patient's unique cancer antigens allows for a personalized treatment approach that may enhance effectiveness.

Therapeutic vaccines for infectious diseases have shown encouraging results in the treatment of chronic viral infections.

- **Combination therapy:** Used in combination with other cancer treatments, such as chemotherapy or immunotherapy, to enhance their efficacy.

- **Adjuvant treatment options:** In many cases subjects may have achieved a best response or reached a disease stabilization point and therefore therapeutic vaccination presents an opportunity to further improve or ameliorate disease or to prevent recurrence of active disease. In HPV5 there are several approved and effective prophylactic vaccination options, but for those infected with HPV and HPV-mediated malignancies the use of a therapeutic vaccine, together with immune checkpoint inhibition and adjuvants, offers significant potential benefit.

Some problems still exist in the development and implementation of therapeutic cancer vaccines:

- **Tumor heterogeneity:** Cancer tissue is highly heterogeneous within a given patient tumor. This heterogeneity can vary greatly between patients. Developing vaccines that target a wide range of tumor antigens is challenging.

- **Immune suppression:** Cancer cells can manipulate the immune system and create an immunosuppressive environment, hindering the effectiveness of therapeutic vaccines. Overcoming this immune suppression is critical for vaccine efficacy.

- **Clinical trial design:** Conducting rigorous clinical trials to evaluate therapeutic vaccines' safety and efficacy is essential for their success. Designing and conducting these trials is complex, requires a specific expertise (medical, scientific, and operational) and can be time-consuming.

In summary, therapeutic cancer vaccines provide a targeted and potentially less toxic alternative to traditional cancer treatments. Ongoing research and clinical trials have the potential to unlock the full therapeutic potential of vaccines in the fight against cancer.

Therapeutic cancer vaccines may become a fundamental part of comprehensive cancer treatment strategies, improving patient survival rates and quality of life.

THERAPEUTIC VACCINES FOR INFECTIOUS DISEASES

Therapeutic vaccines for infectious diseases are developed to stimulate the immune system to recognize and neutralize specific infectious agents, such as viruses or bacteria already present in the body.

The development of therapeutic vaccines for infectious diseases involves identifying specific antigens or proteins that are unique to the pathogen. These antigens are then used to stimulate an immune response targeted against that very pathogen.

Therapeutic vaccines for infectious diseases have shown encouraging results in the treatment of chronic viral infections, such as HIV, hepatitis B, and hepatitis C. These products aim to target viral latency, harness the immune system to control the viral load, reduce disease progression, and improve the patient's overall health.

Furthermore, vaccine treatment approaches in infectious diseases have the potential to make significant global health impacts. In Tuberculosis (TB),[6] there is a significant opportunity to investigate a therapeutic vaccine as an adjunctive treatment or to prevent relapses. Given that TB patients long-term sequelae of disease due to immunopathology is present in a substantial portion of patients, investigating the potential to modify post cure pathology may offer a new path for the more effective treatment.

One challenge in the development of therapeutic vaccines for infectious diseases is the ability to elicit a strong, specific, and sustained immune response. The immune system already may be compromised by the infection, making it more difficult to mount an effective response.

Additionally, the high mutation rate of some infectious agents, such as HIV, poses a problem in developing vaccines that can effectively target evolving strains of the virus.

Despite these issues, therapeutic vaccines for infectious diseases continue to be an area of active research. Clinical trials are being conducted to evaluate their safety and efficacy, and ongoing advancements in the technology have the potential to further enhance their effectiveness.

Ongoing research and development in the infectious disease therapeutic vaccines field – as single or combination therapy – hold the promise of improving patient outcomes and reducing the burden of diseases.

THERAPEUTIC VACCINES FOR AUTOIMMUNE DISEASES

Autoimmune diseases occur when the immune system mistakenly attacks healthy cells and tissues. These conditions can lead to chronic inflammation and damage to various organs. While current treatments for autoimmune diseases focus on managing symptoms and suppressing the immune response, therapeutic vaccines offer a novel approach by specifically targeting the underlying cause of these conditions.

The potential benefit of therapeutic vaccines in treating autoimmune diseases is the restoration of immune tolerance and the rebalance of the immune system. Unlike traditional products, they are designed to target specific self-antigens that are involved in the autoimmune response. By inducing a targeted immune response against these self-antigens, therapeutic vaccines modulate the immune system and restore its normal function.

Ongoing research and clinical trials have the potential to unlock the full therapeutic potential of vaccines in the fight against cancer.

Therapeutic vaccines for autoimmune diseases utilize various mechanisms to achieve their desired effects. These include the following:

- Help induce immune tolerance by promoting the generation of regulatory T-cells (Tregs)[7]: Therapeutic vaccines can dampen the autoimmune response by promoting Treg expansion and activation, which are crucial in suppressing immune responses and maintaining immune balance.
- Antigen-specific[7] immune modulation: Through antigen-specific immune modulation, therapeutic vaccines aim to redirect the immune system's attack away from healthy cells/tissues.
- Immune system reset: This approach involves the use of immune-modulating agents[8,9] or to alter the immune response and restore immune tolerance (i.e., recognize self-antigens as harmless).

Therapeutic vaccines for autoimmune diseases potentially provide targeted and personalized treatment options. Some potential benefits include the following:

- **Disease modification:** By targeting the underlying cause of autoimmune diseases, therapeutic vaccines have the potential to modify the disease course.
- **Personalized approach:** Therapeutic vaccines can be tailored to individual patients, considering their specific immune profiles and disease characteristics. This personalized approach may enhance treatment effectiveness and reduce the risk of adverse effects.
- **Long-lasting effects:** Unlike some conventional treatments requiring continuous administration, therapeutic vaccines may induce long-lasting immune tolerance, resulting in sustained disease control.

However, there are challenges associated with the development and implementation of therapeutic vaccines for autoimmune diseases, such as identifying suitable self-antigens, ensuring vaccine safety and efficacy, and optimizing vaccine delivery strategies.

Therapeutic vaccines may represent a viable option for the treatment of autoimmune diseases by specifically targeting the underlying cause of these conditions.

These vaccines have the potential to provide long-lasting disease control and reduce the reliance on immunosuppressive medications.

CLINICAL TRIALS ON THERAPEUTIC VACCINES: UNIQUE FEATURES

Clinical trials on therapeutic vaccines have some unique features compared to clinical trials for preventive vaccines and "traditional" oncology or infectious disease trials. The following are some key aspects:

- **Patient population:** Clinical trials for therapeutic vaccines typically involve patients who have already been diagnosed with a specific disease, such as cancer or chronic infections. The patient population is often more diverse and may include individuals with varying disease stages, treatment histories, comorbidities, and immune profiles.
- **Study design:** The study design for therapeutic vaccine trials differ from preventive vaccine trials. In therapeutic vaccine trials all participants receive standard of care treatment and vaccine's efficacy is evaluated in combination with existing therapies. This significantly increases the complexity of study design and requires additional management of potential treatments interferences.
- **Trial regulations:** Particular attention must be paid, when designing the study, to the ethics of randomized placebo-controlled trials or add on to standard of care.
- **Endpoints:** The primary endpoints in therapeutic vaccine trials often are focused on clinical outcomes, such as tumor response rates, progression-free survival, or viral load reduction, depending on the disease being targeted. Immunological endpoints, such as immune response measurements, also may be assessed to evaluate the vaccine's mechanism of action.
- **Personalized approach:** Therapeutic vaccines can be tailored to each patient's specific disease characteristics, immune status, and genetic profile. This personalized approach requires careful patient selection, vaccine design and monitoring to ensure optimal treatment outcomes.
- **Long-term follow-up:** Therapeutic vaccine trials often require long-term follow-up to assess the durability of the immune response and evaluate the vaccine's impact on disease progression and recurrence. This extended follow-up period increases clinical development complexity of these products, which might require periodic dosing to boost the immune system.
- **Combination therapies:** Many therapeutic vaccine trials explore the use of vaccines in combination with other treatments, such as chemotherapy, radiation therapy or immunotherapy. Evaluating the safety and efficacy of these combination therapies is an important aspect of clinical trials on therapeutic vaccines.
- **Safety monitoring:** Safety monitoring in therapeutic vaccine trials is crucial, particularly when combining vaccines with other treatments. Adverse events related to the vaccine, as well as potential interactions with other therapies, must be carefully monitored and reported.
- **Laboratory and logistics of study materials:** Vaccines are more sensitive to environmental conditions than small molecules and require extra precautions when transported. Laboratory sample management is more complex and specific assays are required to assess the immunogenicity of the vaccine under investigation.

These unique features reflect the complex nature of therapeutic vaccine development and the need to assess their clinical safety, efficacy and potential benefits in a patient population that already has been diagnosed with a specific disease.

SUMMARY

For the most part, therapeutic vaccines are still in the preliminary stages of development. More research is needed to determine their short- and long-term effectiveness. However, clinical trials have shown encouraging results in treating cancer, infectious diseases, and autoimmune conditions.

Therapeutic vaccines are an exciting area of research that has the potential to revolutionize the way we treat diseases. By harnessing the immune system to recognize and attack specific cancer cells, infectious agents, or self-antigens, these vaccines offer a personalized approach to treatment that can drastically prolong patient's life and improve its quality. ◆

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BIOGRAPHIES

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Dr. Judith Neville serves as an oversight director for therapeutic vaccines within the PPD clinical research business of Thermo Fisher Scientific. She has 25 years of experience in operational management of clinical trials and product development, with a focus on immunology and infectious diseases.

DRUG DELIVERY PLATFORM

VitalDose® EVA Implants for Systemic & Local Delivery of Therapeutics

By: Cyonna Holmes, PhD, Karen Chen, MS, and Brian Duke

LIMITATIONS OF CONVENTIONAL DELIVERY METHODS

As the pharmaceutical development landscape continues to evolve, the search for effective drug delivery technologies continues to be a major driver of innovation. Traditional drug delivery methods, such as oral and injectable formulations, have long been the foundation of therapeutic treatment. However, these approaches have limitations when delivering peptides, biologics, and RNA therapeutics. Innovative drug delivery technologies can help improve drug efficacy, address toxicity issues, and improve patient compliance, which all have potential to improve treatment outcomes.

Systemic delivery approaches that leverage continuous dosing can address adherence issues and improve drug effectiveness while minimizing adverse reactions. Additionally, a localized delivery approach can minimize total drug exposure, reduce off-target toxicities, and overcome targeting issues.

VITALDOSE® EVA IMPLANTS FOR DELIVERY

Polymer-based, durable implants have the potential to overcome the challenges associated with traditional delivery methods for both systemic and localized applications. By providing sustained, continuous dosing, implants may result in better therapeutic outcomes over therapies which require more frequent administration. Because biodurable solutions are not inert and do not degrade, they do not create any degradative byproducts that may cause safety issues.

Durable implants like those composed of VitalDose® EVA, offer tunable parameters including the following:

- High loading (up to 70%) to incorporate large doses and achieve desired drug release per day
- Compatibility across a wide range of molecules from small molecules and peptides to monoclonal antibodies (mAbs) and RNAi therapeutics
- Customized release profiles from months to years
- Extensive selection of form factors and geometries; from rods and rings to films and complex configurations

Biodurable implant solutions can be refilled, replaced, or retrieved (in the case that therapy needs to be interrupted) to achieve systemic or localized delivery across a wide range of therapeutic areas.

SYSTEMIC DELIVERY

Two attributes of EVA which have made it well suited for delivering drug molecules systemically are (1) its high drug loading capability and (2) its straightforward mechanisms for fine tuning drug-release rates. Examples of such mechanisms include changing the vinyl acetate-to-ethylene ratio of the polymer, as well as modifications to the polymer core and membrane formulation design of the implant. These attributes provide continuous systemic dosing over months to multiple years while avoiding an API burst soon after administration, which can be undesirable for some disease treatments.

WOMEN'S HEALTH

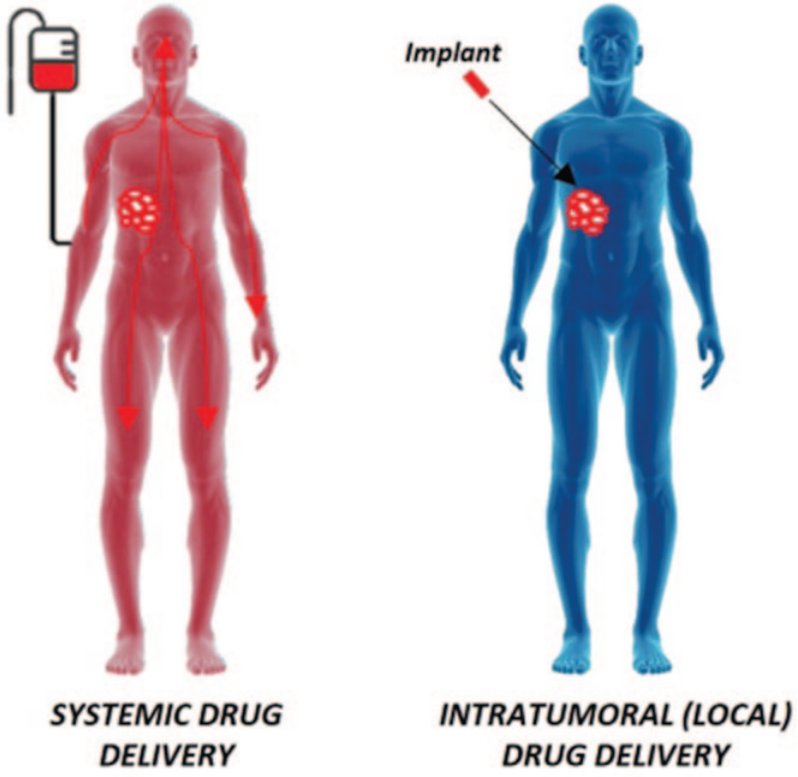
EVA has been used for decades in two contraceptive therapeutics for women. The commercial revenue of these products demonstrates a strong desire from patients for convenient therapeutics with a low dosing frequency.

Nexplanon®, a 2-mm diameter x 4-cm length rod, is implanted via a trocar into the subcutaneous tissue of the upper arm. The therapeutic efficacy of Nexplanon has been observed to be more than 99% effective and it is forecasted to achieve over $1 billion in sales in 2025.[1,2] The product is currently labeled for 3 years of use, but clinical studies are ongoing to study efficacy at 5 years.[3] NuvaRing® is the second contraceptive therapeutic composed of an EVA ring. This ring is self-administered intravaginally every 4 weeks. One benefit of NuvaRing versus oral contraceptive pills is its superior cycle control, which is attributed to its more consistent daily serum levels from continuous dosing, as opposed to daily dosing (NuvaRing daily dosing level of ethyinyl estradiol is half that of oral pill: 15 mcg versus 30 mcg).[4] NuvaRing reached peak sales of $902 million.[5,6]

These commercially well-established contraceptive products have led to EVA's inclusion on the US FDA inactive ingredient database (IID), creating a platform of multiple dosage forms that can be leveraged to deliver drug molecules systemically for therapies other than contraception.[7] For example, an intravaginal ring dosage form is currently being clinically evaluated as a Multi-preventative Purpose Technology (MPT) to provide both contraception and protection against HIV.[8] Intravaginal rings for endometriosis treatment and menopause symptoms are also under investigation.[9,10]

FIGURE 1

Systemic & Local Drug Delivery for Oncology Applications.



ONCOLOGY

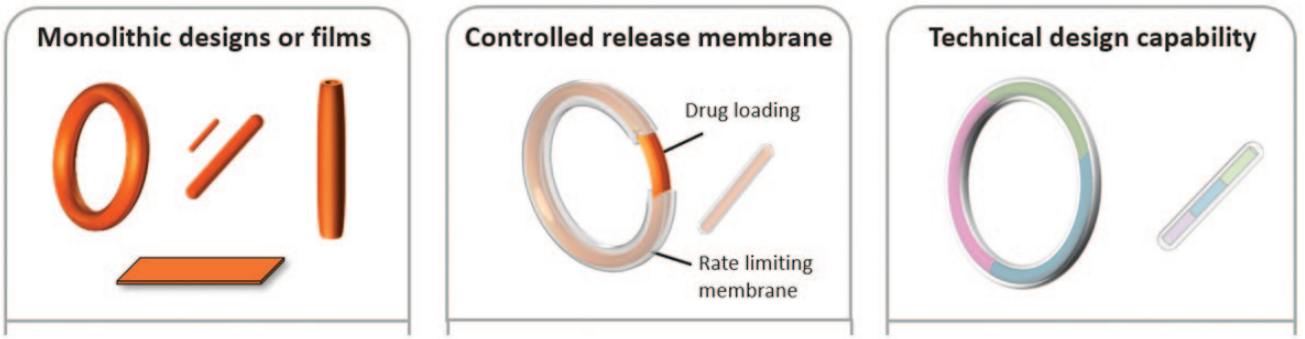
Additional opportunities to improve therapeutic delivery also exist in the realm of delivering systemic adjuvant therapy in oncology. As an example, sustained delivery of hormone therapy can increase patient adherence for both breast and prostate cancer patients. Improved adherence of this type of therapy for both indications can lead to decreased risk of cancer recurrence as well as lower rates of tumor progression. In addition, a lower recurrence risk is linked to increased overall survival rates compared to patients that are less adherent to their therapy. Ultimately, this leads to lower healthcare costs as there is a reduced need for additional treatment interventions and hospitalizations that would be a result of treatment failure.[11]

CENTRAL NERVOUS SYSTEM DISORDERS

Central nervous system (CNS) disorders are often characterized by hard-to-reach targets where drug transport across the blood brain barrier is frequently needed to realize true therapeutic efficacy. In a disease like multiple sclerosis (MS), a range of therapeutic strategies are employed depending on MS type and severity. Treatments range from daily oral medications to longer-acting infusions and injections. For Relapsing-Remitting MS (RRMS) patients with moderate disease taking daily orals, there are limited long-acting options; subcutaneous implants can provide a convenient solution to reduce treatment burden. Reformulations of small molecule oral drugs, like fingolimod or ozanimod, into implants inserted every 6 months, would improve patient convenience and minimize the reminder of dis-

FIGURE 2

Extensive selection of form factors for Biodurable Implants.



ease burden for the patient. For RRMS patients with severe disease, the high dosing requirements and treatment burden associated with some monoclonal antibody infusions could be mitigated by a continuous, lower-dosed implant solution. This approach is not limited to MS. Therapies for other conditions, like Alzheimer's, are often delivered at frequent, high doses to overcome physiological, blood-brain barrier issues. Alzheimer's treatments (approved products and those in development) that are dosed twice a month could be improved with a patient-centric subcutaneous implant with continuous dosing.

LOCALIZED DELIVERY

Localized drug delivery via an implant has the potential to overcome challenges associated with delivering drugs to difficult target sites. Chronic conditions afflicting sites like the eye, brain, or solid tumors face challenges with frequent injections or infusions, large doses, and physiological barriers preventing continuous exposure to the drug at the target site. By situating the implant at or near the target site, a continuous dose can be delivered to maintain therapeutic effect for a prolonged period. This approach may also allow for lower dosing as compared to repeated administration of bolus drug loads.

OPHTHALMOLOGY

In chronic ocular conditions, an implant that elutes drug for over six months mitigates the treatment burden associated with daily eye drops or frequent intravitreal injections. Durable implants, like Iluvien™ for retinal conditions, offer drug delivery for up to 3 years and similar approaches are in development for the treatment of wet age-related macular degeneration.[12,13] Continuous delivery from an implant may also provide increased drug exposure when delivering to areas like the suprachoroidal space. EVA has been used in commercialized ophthalmic implants (e.g., Ocusert, Vitrasert®, iDose® TR) and is currently under investigation for suprachoroidal therapeutics.[14]

Delivery of mAbs, small molecules, or RNAi therapeutics to relevant compartments in the eye offers a patient-centric solution to address low adherence.[15] The proximity of the implant to the target site potentially improves bioavailability and reduces side effects by avoiding drug washout and off-target delivery. Durable implants mitigate tear turnover, blinking, and corneal and conjunctival barrier issues that result in low therapeutic efficacy of eye drops. Recently approved iDose TR (Glaukos), is a ~0.5-mm diameter by 1.8-mm implant that incorporates a VitalDose EVA membrane into a titanium implant structure.[16] The VitalDose EVA membrane allows for continuous prostaglandin release and is designed to deliver up to 3 years of drug therapy.[17] Biodurable treatment approaches may also lessen healthcare resource utilization and cost burden associated with frequent visits.[18]

ONCOLOGY

In a similar fashion, localized drug delivery in oncology has been gaining strong momentum in the treatment of solid tumors across multiple indications. The localization via an implant dosage form can provide physical targeting of the drug directly to the tumor site (Figure 1). Not only can this enhance the delivery of oncology therapeutics that lack molecular targeting abilities, but this can also compliment drugs with built-in targeting, such as antibody or peptide drug conjugates or bispecific antibodies, enhancing their molecular targeting with the added physical targeting benefit. This will allow the confinement of the treatment to the site of the disease which can ultimately minimize total drug needed while maximizing efficacy and reducing adverse effects.[19]

In addition, an implant delivery system can provide modified release kinetics to slowly release drug into the tumor to cir-

cumvent rapid tumor leakage that is often seen with repeated intratumoral injections.[20]

SUMMARY

Traditional drug delivery methods (oral and injections) face limitations within today's landscape of complex drug development. These limitations include but are not limited to stability, absorption, and degradation issues related to oral administration and frequency of injection administration. VitalDose EVA implants offer a valuable solution by providing sustained, continuous dosing that can overcome formulation limitations. Its capabilities for high drug loading enables medication to last for months or even years which can significantly reduce the burden of frequent dosing while optimizing patient freedom and adherence. In addition, VitalDose EVA demonstrates broad compatibility with a wide range of drug molecules and possesses significant design flexibility to suit different administration routes for patient-centric drug products.

VitalDose implants have been commercially validated in both contraceptive and ophthalmic indications, and the drug delivery platform shows further promise across a wide range of indications for both systemic and localized drug delivery. ◆

Nexplanon® and NuvaRing are registered trademark of N.V. Organon; Celanese is not affiliated with nor sponsored by N.V. Organon.

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BIOGRAPHIES

Dr. Cyonna Holmes earned her PhD in Biomedical Engineering from the University of Texas Southwestern Medical Center (Dallas, TX) and her BS in Bioengineering from Stanford University (Stanford, CA). At Celanese, she serves as Global Strategy Lead for Ophthalmology, Rare Diseases, and RNA Therapeutics. She has experience in the areas of drug delivery, lifecycle management strategy, new product development, and market entry strategy. She has published articles in peer-reviewed journals.

Karen Chen earned her MS in Formulation Science from Fairleigh Dickinson University (Teaneck, NJ) and her BS in Biology and Chemistry from Rutgers University (New Brunswick, NJ). At Celanese, she serves as Global Strategy Lead for Oncology, Obesity, mAbs and peptides. Her experience spans new product development as well as market entry and expansion strategies for functional excipients and drug delivery.

Brian Duke earned his BS in Industrial Engineering from Texas A&M University (College Station, TX) and his MBA from Pennsylvania State University (State College, PA). At Celanese, he serves as Global Strategy Leader for Women's Health and Bioresorbable Technologies. His professional experiences have primarily focused on marketing & sales of polymers for pharmaceutical and industrial applications, as well as business strategy development focusing on external partnerships and operating models.

Drug Development
EXECUTIVE

Fady Boctor

President & Chief Commercial Officer

Petros Pharmaceuticals

Petros Pharmaceuticals & Self-Care: Expanding Access to Rx Products Through a Tech-Powered OTC Pathway

Petros Pharmaceuticals is focused on expanding consumer access to medication through over-the-counter (OTC) drug development programs. The company is in the process of bringing its current lead prescription (Rx) erectile dysfunction (ED) therapeutic OTC while developing a pathway that would take future therapeutics OTC as well. Petros is a pure play in the Rx-to-OTC self-care market, which is rapidly growing, and has a mission to empower patients to take better control of their health.

Drug Development & Delivery recently interviewed Fady Boctor, President and Chief Commercial Officer at Petros Pharmaceuticals, to discuss the process of taking a product from Rx-to-OTC, the benefits and challenges of the process, and the future of the marketplace.

Q: Can you give an overview of how medications go from Rx-to-OTC?

A: It predominantly becomes a process of comprehension and the consumer behavior associated with it. Those are the core principles. There are three distinct studies that need to be completed, which have to do with comprehension, self-selection behavior, and actual use without a prescription. The first is a Label Comprehension Study, which once completed, allows companies to improve and enhance a label that is ultimately well understood by the laymen consumer.

Next is the Self-Selection Study, which brings that new and optimized label to men and women (also known as all-comers) and allows them to review the label and select whether or not to use the product. The study is reviewed to see whether the participants appropriately self-selected based on gender, medical disposition, and history. The comprehension becomes behavioral in this step.

The last study is the Actual Use Study/Actual Use Trial, which is akin to a Phase

3 clinical trial. The participants read the label, self-select, and use the product in a simulated OTC setting. This is the most expensive portion of the pathway and requires approval or pre-clearance by the FDA to conduct.

Along this pathway, there are numerous iterations to optimize the steps. And recently, there is a new frontier with technology and devices emerging, hence the FDA introducing and proposing Additional Conditions for Nonprescription Use (ACNU), which will enable companies to offer various resources (among them technology assistive tools such as apps) enhancing the appropriate and safe use of their Rx-to-OTC switch candidate. With these additional tools will come the necessity to conduct Human Factor Studies, assessing whether the consumer is able to navigate the app as intended.

Currently, the default for bringing a product OTC does not necessitate any additional tools, unless proven necessary. Only after a company shows the study participants have failed to comprehend and/or comply with a label is technology introduced.

For those who may be familiar with Risk Evaluation and Mitigation Strategy for prescription medications, also known as REMS, ACNU may be considered akin for certain Rx-to-OTC switches to come. This would potentially establish a new corridor for prescription to OTC switches in the future.

Q: What are the benefits of a product going from an Rx to an OTC availability?

A: The most pronounced benefit is expanded access enabling more people to use a particular therapy. The hurdles and burdens of having to make a doctor's appointment and go to the appointment (whether in-person or virtually) are removed when a product goes OTC. The Consumer Healthcare Products Association (CHPA) is an advocate in this area and one of their case studies focuses on smoking cessation products. The utility of those products was somewhat meek when they were Rx. However, once they were switched to OTC, there was a 150%-200% increase in use during the first year of their switch. This impacted overall healthcare costs significantly, as smokers attempted to quit smoking, and whether they completely stopped or reduced their use, their outcomes were improved.

Another benefit is the potential for greater education. Taking a product OTC allows companies to educate a patient about the broader implications and progression of their condition. For example, a gentleman might not know that he has a serious heart issue if he is experiencing ED, and reading about it on a label or learning more via a web app during purchase may help enlighten him to seek appropriate evaluation and treatment.

Self-care is a growing market and having products available OTC empowers consumers.

Q: What is the market for Rx-to-OTC products? Can you provide examples of successful transitions?

A: The Rx-to-OTC switches market is rapidly growing. In 2023, it had a valuation of $38.7 billion, according to FMI's Rx-to-OTC Switches Market Outlook. The report projects that this market will reach $66.5 billion by 2033.

There are many examples of successful Rx-to-OTC transitions. Some notable ones in 2023 were Opill, a birth control pill, and Narcan, a naloxone hydrochloride treatment for known or suspected opioid overdose. Others within the past 20 years include Nexium 24 HR, Flonase Allergy Relief, Zyrtec, Plan B, and Prilosec OTC. Additional ones can be found on CHPA's Rx-to-OTC Switch List website.

Q: What is significant about Petros' lead ED therapeutic going OTC?

A: It is important to note there are currently no clinical comparative data among the class of phosphodiesterase 5 Inhibitors (PDE5Is). Petros' lead ED therapeutic hosts a distinct label, specific to its clinical trials, which also remains branded and patent-protected, encouraging ongoing development and investment, making it worth our company's time. We are the New Drug Application (NDA) holder, and it is an added benefit we are taking the product OTC with the NDA in our possession.

Lastly, we believe the consumer education component is very important for any product that switches to OTC. There is an opportunity here to educate consumers and their advocates around broader health implications, awareness, and potential concerns. We intend to leverage our emerging OTC technology platform to help people learn more about their potential health issue and possible correlated comorbidities with actionable follow-up suggestions, while purchasing or engaging with their OTC therapy of interest.

Q: Can you discuss your process for taking the product OTC?

A: We are following the previously mentioned protocol. Additionally, we've developed our own scientific advisory committee. In many respects, they act and serve as an internal arms-reach FDA representation. The committee gives us the FDA perspective from a legal, regulatory, and clinical perspective. We have found this to be very productive and contributory and have had the committee attend many of our FDA meetings. We are not moving along the OTC pathway in a vacuum but are garnering guidance from this committee.

Our process also goes beyond a technology assistive tool, which we believe is a baseline feature. We are attempting to go beyond by seeking to integrate elements of AI addressing specific concerns that the FDA has communicated to us quite consistently. These include validating the patient, ensuring they are male, and that they are 18+ with ED.

We believe both of these – a scientific advisory committee and the use of AI to address FDA concerns – are emerging best practices.

Q: What are the greatest hurdles in switching a product from Rx-to-OTC?

A: We have identified three hurdles. First, the FDA is the greatest hurdle. However, I want to note what they do is necessary. They pressure test us and seek to answer critical questions of safety, especially around the anomalies. The greatest limiting factor is making sure we address their concerns, while forging ahead on a reliable and credible path forward. And even with a solid plan, there could be a shift in the plan/ideology at times, which could delay and require duplicative work. This is the second hurdle and is always on every sponsor's mind.

The third biggest hurdle is budgetary constraints. It is important to be well-funded to do the quality work that needs to be done, and to appropriately use the funds accordingly.

Q: Where do you see the Rx-to-OTC market in the next 10 years?

A: Exciting things will happen in the next 10 years. As we see from the FMI statistic, the Rx-to-OTC market is set to nearly double throughout the next 10 years. We can see uncomplicated blood pressure medications, anti-depressants, single-dose antibiotics for uncomplicated urinary tract infections, statins, etc. possibly becoming available without a prescription. If somebody has consistent high blood pressure, for example, and begins to use an OTC treatment option, it may have a positive impact and ultimately a tremendous value to public health. Likewise, pre-diabetes and low-/early-stage diabetes products may also become OTC candidates. Combination oral contraception may become available – we believe Opill is just the beginning.

All of these will reduce US healthcare costs, increase proactive engagement with the healthcare landscape by the patient-consumer, and provide for an empowered self-care culture driven by US patient-consumer. Many of these conditions are reasons for common visits to primary care facilities, which are often schedule-prohibitive resulting in significant hurdles and delays in treatment. This Rx-to-OTC self-care landscape may help reduce a variety of bottlenecks and burdens in the healthcare system.

Q: Do you believe more products will go directly OTC when they are being developed?

A: If the prescription OTC space matures well enough, and there is a strong American awareness of general primary care and therapeutics available OTC, then I believe sponsors will prefer OTC vs. Rx.

There are a lot of complexities with developing new prescriptions. Sponsors of prescription therapies will often market to physicians, partner/contract with insurance companies/Pharmacy Benefit Managers (PBMs), attend practitioner conferences, utilize a large sales force, often issue coupon and voucher programs, as well as market directly to the patient-consumer (DTC); this is a remarkably costly investment.

By going OTC, sponsors of prescription-grade therapeutics may educate physician and consumers, but they do not need to partner with PBMs, and they do not need to offer coupons as long as their price is competitive. They can focus on treatment education, collaborate with pharmacies and distribution channels, and meet the patient-consumer in the same aisle and/or web landing page as their preferred shopping channels.

Launching a product OTC makes for a far more controllable, streamlined, and convenient process, which is attractive to sponsors and patient-consumers alike. And with the growth of the self-care market, companies may be more focused on going direct-to-consumer versus building an entire infrastructure to take their Rx products OTC. ◆

Special Feature

Excipients: Advanced Biologics Require Innovative Excipient Science

By: Cindy H. Dubin, Contributor

The pharmaceutical excipients market was valued at $10 billion in 2023 and is expected to reach almost $14 billion by 2028. Major factors impacting demand are increased R&D investments in novel excipients and growing emphasis on patient-centric formulations.[1] Additionally, superior generics and biosimilars are driving demand for novel excipients and drug delivery platforms, which enable differentiated products for chronic diseases, repurposed drugs for new routes of administration.

Novel excipients can play a critical role in achieving challenging technical targets that are not possible with traditional excipients alone, says Nick DiFranco, MEM, Global Market Manager, Novel Pharmaceutical Technologies at Lubrizol. Novel excipients may also provide intellectual property protection — both in the form of excipient licensing and formulation-specific IP tied to a drug product. The combination of technical and commercial benefits provided by novel excipients ensures formulators can meet their target product profile and develop products that have significant market potential, he says.

Additionally, the 505(b)(2) regulatory pathway in the United States (and its European counterpart, the hybrid procedure) has created an appealing source of innovation in the field of small-molecule drugs. "By leveraging existing safety and toxicity data for approved drugs, pharmaceutical companies can reduce risk and streamline their path to market for drug reformulations for chronic diseases such as cancer and diabetes," says Mr. DiFranco. "505(b)(2) products can take several forms, such as changes to formulation ingredients or routes of administration. The motivations behind 505(b)(2) product development include improving patient adherence with easier-to-dose products and optimizing properties such as drug delivery efficiency and side-effect profile.

Super Refined™ excipients (Croda Inc.)

Regarding the latter, industry is working to address issues of adverse reactions, interactions, or contraindications that may result from excipients. A recent case involved EG/DEG-contaminated over-the-counter medicines, which alerted worldwide regulatory agencies to create guidelines for determining EG/DEG content in relevant raw materials/excipients.

"Physical and chemical reactions between excipients and APIs are inherent in the drug development process," says Nitin Swarnakar, M Pharm, PhD, NA Applications Lab Manager Pharma Solution, BASF Corporation. "However, to minimize the potential negative effects of excipients, such as adverse reactions, interactions, or contraindications, several strategies are being employed." He suggests following ICH M7 and ICH Q3B(R2) guidelines to provide a framework for determining safe limits of mutagenic compounds and impurities in pharmaceutical products. "Adhering to these guidelines helps establish acceptable thresholds to minimize adverse effects associated with excipient usage." Additionally, collaborate with excipient manufacturers to address concerns related to drug-excipient interactions, choose reliable excipient suppliers, and optimize dosage form parameters.

"Quality, high-performance excipients are at the heart of every successful formulation," says Kurt R. Sedo, Vice President Operations, PharmaCircle, which offers an integrated data and analytical enterprise solution. "As the industry continues to develop more challenging "traditional" molecules and expand new modalities into advanced biologics, there will be an increasing need for innovation in excipient science to enable these products to be successfully developed."

This exclusive *Drug Development & Delivery* annual report features the novel and functional excipients being developed, the role they will play in reformulations and new formulations, and their versatility in drug delivery.

ABITEC Corp.: Formulating Functional Lipids as SEDDS

Most novel active pharmaceutical ingredients (APIs) currently being developed are low-soluble (BCS Class-II), low-permeable (BCS Class III), or both (BCS Class IV). For this reason, highly functional excipients capable of addressing these challenges are needed. ABITEC develops and manufactures highly functional lipids for the pharmaceutical, nutraceutical, and specialty chemicals industries. These excipients include medium chain triglycerides, mono- and diglycerides, pegylated esters, and hydrogenated vegetable oils. ABITEC functional lipids can be formulated as self-emulsifying drug delivery systems (SEDDS) that are of significant utility in improving the bioavailability of various APIs.

Recently, ABITEC launched a novel co-processed excipient system, ABISORB-DC™, designed to allow the direct-compression tableting of liquid lipid preconcentrates, including SEDDS preconcentrates. John Tillotson, RPh, PhD, Technical Business Director – ABITEC Corporation, says: "This excipient allows for the bioavailability enhancing features of lipid-based drug delivery to be readily combined with the ease of formulation and manufacturing of direct-compression tableting at industry tableting speeds."

He goes on to explain that excipients can often be employed to allow for dosage form transition from higher cost dosage form manufacturing processes to lower cost dosage form manufacturing costs. For example, transitioning from a liquid-filled hard gelatin capsule or liquid-filled soft gelatin capsule allows for the transition from a lower throughput unit operation to a higher throughput unit operation, which can reduce costs both in the manufacture and formulation of the dosage form.

"While the utility of liquid lipids in the formulation of low-soluble and low-permeable active pharmaceutical ingredients is well known, these dosage forms, including SEDDS, have been largely restricted to liquid-filled hard gelatin capsules and liquid filled soft gels," Dr. Tillotson says. "Typically, these dosage forms are less economical, and often, due to ingredient migration between the capsule and fill, are more difficult to formulate and less stable than tablets."

The issue with tableting the functional lipids is that the oily nature of the lipids interferes with the bonding characteristics of the tableting ingredients during compaction, resulting in non-robust tablets. ABITEC recently launched a co-processed excipient system that allows for the ready compaction of liquid lipids, including the components employed in a SEDDS system. The ABSISORB-DC system allows for the compaction of SEDDS, thereby combining the bioavailability enhancement of SEDDS formulations with the economy and stability of direct-compression tableting.

As a result of the complexity of optimally developing SEDDS, ABITEC developed a formulation and screening tool, the ABISOL™ Emulsion Preconcentrate Kit. This formulation tool is intended to assist in the fast tracking of SEDDs formulation development with new APIs. The kit contains five separate emulsion preconcentrates for use in the creation of API carrying SEDDS preconcentrates, and was developed by varying functional lipids with dif-

ferent HLBs employing a D-Optimal response surface optimization of solubility and emulsion characteristics to formulate the five emulsion preconcentrates.

Recently, a CRO customer was tasked with the solubilization and per-oral delivery of a BCS Class II API to conduct API toxicology and dosing studies. The CRO was experiencing difficulty solubilizing the API. They obtained an ABISOL Kit and screened the active, employing the kit preconcentrates. The CRO was able to identify preconcentrate V as providing the greatest degree of solubility with the API, as well as providing for the desired emulsion characteristics. "Employing preconcentrate V to dissolve the API allowed for the per-oral dosing and continued study with the BCS Class II API," says Dr. Tillotson.

Actylis: Enhancing the Efficacy of Finished Drugs

The demand for superior generics and innovative drug delivery systems drives the exploration of novel excipients. These excipients enable the development of differentiated products for chronic diseases, repurposed drugs for alternative routes of administration, and novel drug delivery platforms. By incorporating the high-quality excipients, customers can enhance the efficacy of their finished drugs. Through strategic selection and innovative use of excipients, finished drug manufacturers can overcome development challenges, reduce costs, and drive therapeutic innovation.

As the industry continues to evolve, companies like Actylis continue to play a pivotal role, offering a range of excipients in several grades, suitable for many pharma and biopharma finished drugs.

"Excipients, often overshadowed by the active pharmaceutical ingredients, play a crucial role in the formulation of drugs," says Kate Buggle, Director of Biopharma Sales, Europe, Actylis. "Understanding the significance of excipients is paramount in optimizing drug formulations and addressing the challenges faced by the pharmaceutical industry."

Binders, for instance, hold the ingredients together in a tablet or capsule, ensuring uniformity and coherence. Fillers add bulk to formulations, facilitating accurate dosing and aiding in the compression process. Disintegrants promote the breakup of tablets, enabling efficient dissolution and absorption in the body. Lubricants prevent sticking of the formulation to machinery during manufacturing and to the gastrointestinal tract upon ingestion. Solvents assist in dissolving APIs and other excipients, facilitating homogeneity.

Rising development costs pose a challenge to the pharmaceutical sector. Excipients offer a cost-effective solution by optimizing formulations, reducing the quantity of expensive APIs required while maintaining efficacy. Moreover, excipients enhance process efficiency, minimizing production expenses.

"We work closely with our customers to custom develop excipients formulations, so they can achieve cost savings without compromising quality," she says.

While excipients enhance drug performance, they may also pose risks such as allergic reactions or interactions with other medications. To mitigate these risks, extensive safety assessments are conducted during excipient selection and formulation development. Regulatory bodies mandate thorough testing to ensure excipient safety and compatibility with APIs. Ms. Buggle says that pharmaceutical manufacturers need close collaboration with suppliers to solve those challenging quality, innovation or supply chain issues that can delay to-market plans. A deep understanding of those challenges is critical to minimize those delays.

BASF Pharma Solutions: See How Formulators Choose the Right Excipients

BASF Pharma Solutions specializes in a range of pharmaceutical excipients that offer various functionalities and benefits for drugs. These excipients play a crucial role in ensuring the stability, effectiveness, and ease of administration of APIs, says Nitin Swarnakar, M Pharm, PhD, NA Applications Lab Manager Pharma Solutions, BASF Corporation.

"For drugs with acceptable physiochemical properties (like particle size, density, flow, and tabletability) belonging to DCS-I and DCS IIa, we recommend co-processed excipients like Ludipress® (Lactose, povidone, crospovidone), Ludipress LCE, Ludiflash® (mixture of D-mannitol, crospovidone, polyvinylacetate, povidone), and All-In-One excipients like Kollitab™ DC 87 L (Lactose Monohydrate, Crospovidone, PEG-PVA-Copolymer, Sodium stearyl fumarate)," he says. "These co-processed excipients combine multiple ingredients to create a single, optimized excipient with enhanced functionality. They offer significant time-saving benefits in the development, analysis, and blending of pharmaceutical blends, accelerating the rapid development of dosage forms."

For drugs with poor particle size and tabletability, BASF utilizes binding agents such as wet binder povidone-30, polyvinyl alcohol-polyethylene glycol copolymer (Kollicoat® IR), povidone-90 (Kollidon® 90

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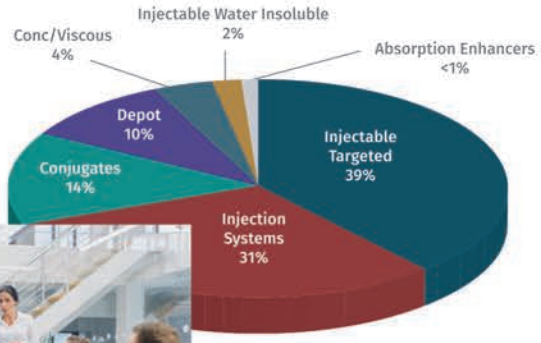
Excipient vs Strength	375 mg telaprevir
HYPROMELLOSE ACETATE SUCCINATE 12070923 (3 MM2/S) **(Core/Content)**	375 mg
SODIUM LAURYL SULPHATE (Core/Content)	7.58 mg
DIBASIC CALCIUM PHOSPHATE ANHYDROUS **(Core/Content)**	75.76 mg
CROSCARMELLOSE SODIUM **(Core/Content)**	30.3 mg
MICROCRYSTALLINE CELLULOSE **(Core/Content)**	75.76 mg
SODIUM STEARYL FUMARATE **(Core/Content)**	29.29 mg
COLLOIDAL SILICON DIOXIDE **(Core/Content)**	7.58 mg
POLYVINYL ALCOHOL, UNSPECIFIED **(Tablet/Capsule coat)**	11.72 mg
POLYETHYLENE GLYCOL **(Tablet/Capsule coat)**	5.92 mg
TALC **(Tablet/Capsule coat)**	4.33 mg
FERRIC OXIDE YELLOW **(Tablet/Capsule coat)**	0.32 mg
TITANIUM DIOXIDE **(Tablet/Capsule coat)**	7 mg
FD&C RED NO. 40 **(Tablet/Capsule coat)**	
FD&C BLUE NO. 2 **(Tablet/Capsule coat)**	

Evaluate New and Promising Technologies



Injectable Drug Delivery Technologies

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evo), and dry binder like copovidones (Kollidon VA 64 fine). These agents help hold the drug particles together, ensuring the tablet remains intact upon compression, says Dr. Swarnakar.

To address the challenge of poor solubility of drugs in biological fluids, BASF uses various solubilizers options. These include a range of surfactants such as Soluplus®, ethoxylated solubilizers, poloxamers, polysorbates, and sorbitan Esters. "We also utilize solubilizers based on solvents like low molecular weight polyethylene glycols (PEGs) and complex forming agents such as povidone and copovidones," he says. "These solubilizers are carefully selected to enhance drug solubility and improve therapeutic outcomes."

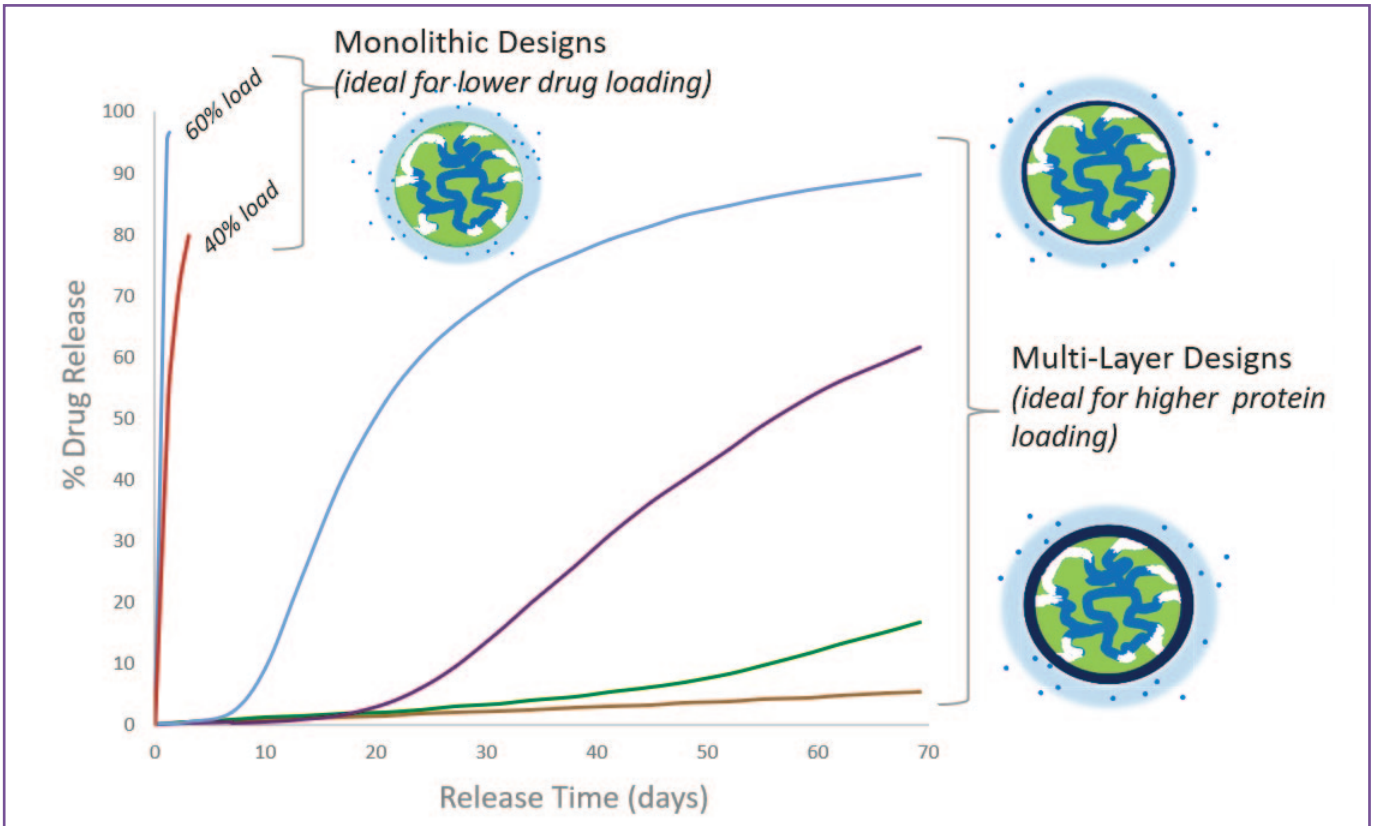
And, for drugs that may not remain stable under storage conditions, formulators utilize specific coating polymers like polyvinyl alcohol-polyethylene glycol graft copolymer and polyvinyl alcohol (PVA) (Kollicoat Protect) or Methylmethacrylate–diethylaminoethylmethacrylate copolymer (Kollicoat Smartseal 30 D). These coating polymers offer moisture barrier applications and ensure stability, extending the shelf life of the drug.

In cases where a drug degrades in the harsh gastric environment upon oral administration, BASF employs enteric coating techniques. This protective coating ensures the drug remains intact until it reaches the desired site of action, enhancing stability and therapeutic effectiveness. For potent drugs with short elimination half-lives, sustained-release polymers, like polyvinyl acetate (Kollicoat SR 30 D), hydroxy propyl methyl cellulose, ethylcellulose in matrix or reservoir type systems, are used. These systems are designed to release the drug gradually over an extended period, maintaining therapeutic levels in the body and optimizing treatment outcomes.

Celanese: Versatile Platform for Controlled/Sustained Release

Providing continuous long-acting drug release is a growing area of research with the potential to improve treatment for chronic diseases. VitalDose® EVA copolymer from Celanese is a biocompatible, biodurable, and adaptable technology designed for use in long-acting injectables and drug-eluting implants. It functions as a versatile platform for controlled and sustained drug release. It allows for a high drug load in the dose form and enables the design of drug release profiles lasting from months to years – including very water-soluble drugs. Thus, VitalDose EVA can cater to various treatment needs, says Christian Schneider, PhD, Application and Business Development Leader at Celanese.

In addition, the material's versatility allows it to be compatible with a range of



VitalDose® EVA flexible design capabilities enable formulation ease with highly tunable release rates to achieve the target dosing kinetics for small and large drug molecules (Celanese).

drug types, including complex biologics, RNA, small molecules, and peptides. Monolithic designs highly loaded with a large, very hydrophilic protein, release very fast due to a high degree of porosity inside the EVA matrix. By adding well-designed rate control membranes to the highly loaded monolithic designs, the retention of the protein is significantly increased and the protein release can be adjusted to meet the target rates. Dr. Schneider says: "This compatibility opens doors for the development of new and diverse therapeutic options in the areas of ophthalmology, oncology, and women's health."

Dr. Schneider adds that VitalDose EVA properties hold promise for driving advancements in several areas of drug delivery, particularly when it comes to continuous systemic delivery for chronic diseases. Its ability to maintain sustained and controlled drug release profiles over extended periods allows for less frequent dosing. This can potentially improve patient adherence and may lead to better outcomes, reducing the healthcare burden for conditions requiring consistent medication.

"Furthermore, the potential for improved efficacy and safety using EVA paves the way for repurposing existing drugs with limitations in traditional formulations," says Dr. Schneider. "By enabling alternative routes of administration, such as localized implants, EVA could enhance a drug's therapeutic effect while minimizing side effects. This can potentially extend drug patent life and offer opportunities for further research and development."

Croda Inc.: High Purity Excipients for Drug Delivery & Drug Stability

Therapeutic proteins, such as monoclonal antibodies (mAbs) and other biosimilars, are usually dosed via parenteral administration to patients. However, due to their inherent instability in the liquid state, many of these products require the use of a surfactant such as a polysorbate. Surfactants are widely used to prevent protein aggregation during manufacturing, freeze/thaw stress, shipping agitation, and upon long-term storage.

"Polysorbates and other non-ionic surfactants weakly bind to proteins via interaction of the hydrophobic regions of the protein and the hydrophobic chain of the polymers, which results in a tendency to solubilize proteins," says Andrew Bright, Technology Specialist at Croda. "This weak interaction can slow, reduce, minimize, or prevent hydrophobic regions of the protein molecules interacting and forming aggregates, thus preserving their activity. Polysorbates can also coat the container wall and can be present at the air-water interface, which can prevent the protein interacting with these interfaces, thereby stabilizing the protein."

He explains that small-scale bioprocessing manufacture can be expensive. Adding to the small-scale manufacturing expenses are the costs of analytical testing and labor. Many organizations conduct initial screening experiments with multiple excipients when developing new therapeutic mAb formulations; surfactants, cryoprotectants, and pH buffer conditions may also be screened to establish best materials and lead formulation conditions to take into further development.

"Several issues can arise during the initial formulation screening, including the use of low-grade or expired excipients (usually used to reduce cost), the use of excipients from different suppliers with wide monographs, and excipients with large batch-to batch-variations," says Mr. Bright. "Depending on the source, the age, and grade, the same excipient may have different properties and impurity profiles, thus leading to a variety of different results, as some degradation may occur at a very slow rate, with some issues being only identified after several months of study."

The above-mentioned factors could lead to the formulator being pushed in the wrong direction when exploring excipient options and types for the therapy and repetition of testing, thereby increasing the time required to establish a suitable formulation for use. "This is why the use of high purity excipients like SR Polysorbates and other high purity excipients in a formulation are critical," he says.

Variations in polysorbates can affect formulation performance, too, as different grades and suppliers of polysorbate have different levels of impurities that can have unwanted interactions, degradation of the proteins, and performance. Croda makes model formulations and evaluates different excipient grades to determine their impact on model API stability. This can usually be used to advise impact of excipient grades. Mr. Bright says: "We can evaluate such performances of different grades of excipients in our formulations and biological applications labs."

Croda's Super Refined™ excipients undergo a proprietary purification process, removing excipient impurities and producing a narrow monograph, ensuring consistent performance between different batches, which in turn, ensures that the results obtained for the final clinical or commercial formulation are the same as those obtained during initial excipient screening studies.

Curia: Excipients are the Great Problem Solver in Parenteral Development

Since the Covid-19 pandemic, the influx of more complex formulation design has emerged to deliver more sensitive payloads. Protection of labile therapeutics agents in advanced drug delivery systems, such as liposomal and lipid-nanoparticle (LNPs), are seeing increased numbers of LNP drug products undergoing successful Phase 1 trials (and beyond), year-on-year. "Curia is working with clients to develop LNP formulations where the novel design is in the ionizable lipid, but have found that selection of the right PEG-functionalized lipid has a multitude of benefits," explains Jaclyn Raeburn, PhD, Manager, Formulation Development, Glasgow, Curia. "Utilizing a shorter C14 vs C18 chain PEG-functionalized lipid LNP allows for shorter dissociation and, therefore, increased efficacy."

Curia's capabilities encompass guiding molecules from the lab to first-in-human trials and eventual commercialization. Many of the synthetic small-molecule APIs Curia's clients are progressing for pre-clinical/Phase I studies show poor aqueous solubility. She says that looking to organic solvents to immediately offer solubility for tox studies, but downstream this can have regulatory issues. She explains that small-molecule APIs frequently degrade via oxidative pathways, making stabilizing excipients crucial to reducing oxidative decomposition in solution. Excipients may scavenge oxygen, preventing oxidative decomposition; or like EDTA, chelate metal ions catalyzing decomposition.[2]

"We reformulated a drug product for a client where discoloration was a concern, using EDTA," she says. "It was shown to decrease the rate of discoloration on storage, further enhanced by nitrogen headspace to diminish residual oxygen content. The choice of grade of a particular solubilizing/stabilizing excipient is also key to mitigating oxidative decomposition and improving overall drug product performance. We use surfactants such as polysorbate 20 and 80 or PEGs to improve solubility, but have seen improved long-term stability with super-refined grades of such excipients."

In the development of sustained-release formulations, viscosity becomes a fundamental attribute during excipient selection. Biocompatible polymers such as carboxymethylcellulose sodium (CMC Na), acacia, sodium hyaluronate, and biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), are utilized for sustained release due to their tunable properties[3] in the polymer-drug matrix. Curia has developed many drug products with common water-soluble polymers, like PEG400 and PEG4000, to increase viscosity. Dr. Raeburn says: "Often, a client is targeting viscosities >20mPa.s, which requires a substantial concentration of such excipients. This will impact tonicity and bring regulatory concerns. Our clients expect innovative design to solve their formulation issues – we look to biocompatible polymers to achieve higher viscosities while maintaining a firm regulatory position."

Where solution stability is a particular concern, lyophilization is an option; introducing additional excipient classes like cryoprotectants, lyoprotectants, and bulking agents. Bulking agents, often non-reducing sugars like sucrose or trehalose[4], enhance lyophilized solid cake integrity and reconstitution ability. Lyoprotectants ensure stability during the lyophilization process, preventing microstructural collapse and subsequent moisture uptake on storage.[5]

"Mannitol is recognized as ubiquitous in lyophilized products, but itself is crystallizable into multiple polymorphic forms, and an amorphous bulking agent/lyoprotectant would simplify development," she says. "Replacing with sucrose, for example, can reduce lyophilization cycle time, but maintain structural and chemical integrity of the lyophilized drug product."

CycloLab Ltd.: SBECD's Versatility in Drug Delivery

Today, more than 250 active ingredients or their combinations formulated with cyclodextrins, including 150 with beta-cyclodextrin (betadex), are available throughout the world. There is a growing tendency in the number of approved pharmaceutical formulations containing an anionic modified cyclodextrin, referenced in US Pharmacopoeia as betadex sulfobutyl ether sodium or sulfobutylbetadex sodium in European Pharmacopoeia (SBECD, marketed under brand names Captisol or Dexolve).

"SBECD is a versatile excipient that can significantly improve the solubility, bioavailability, and stability of APIs," says Dr. Éva Fenyvesi, Senior Research Scientist at CycloLab.

The stable solutions are usually intended for intravenous or intramuscular use, but other administration routes, such as buccal, vaginal, nasal, ophthalmic, and dermal have also appeared in the literature containing more than 700 scientific papers (Elsevier Scopus database). She explains: "Various nano-formulations containing SBECD have been studied to utilize the inclusion complex forming (solubilizing, stabilizing) ability of this CD derivative

in synergy with the benefits of the nano-sized particles/droplets."

For example, nanoparticles formed by self-assembly of chitosan with positive charge and SBECD with negative charge were thoroughly studied for various drugs, such as econazole nitrate, hydrocortisone, famotidine, besifloxacin, and naringenin to get sustained-release formulations with enhanced solubility and bioavailability. The chitosan/SBECD nanoparticles were found effective in targeted and controlled delivery of not only the small molecular drugs, but for protein drugs. Chitosan/tripolyphosphate nanoparticles with drug/SBECD complex were found biocompatible and biodegradable providing increased drug release for Docetaxel. Nanoemulsions (nanodroplets) stabilized by various surfactants (Kolliphor® HS 15, Tween 80, poloxamer 407, and polyethylene glycol 400) have similar advantages for voriconazole and carnosic acid. As a novel drug delivery system, pH-responsive nanoparticles, based on SBECD and cetylbenzyldimethylammonium chloride, showed assembly and disassembly behaviors with the pH alternating between 10.0 and 2.0, thus enhancing the anticancer efficiency of anticancer drug – celastrol – Dr. Fenyvesi explains.

Additionally, consider the following: Chemically cross-linked SBECD nanoparticles using diisocyanate type cross-linking agent can capture and gradually release the active ingredients – such as moxifloxacin; hydrogels consisting of SBECD and hyaluronic acid have good biocompatibility and provide prolonged drug release for lidocain as a long-lasting analgesia therapeutic; thermoreversible nasal *in-situ* gel of drug/SBECD complex in alginate gel was suggested for nasal application of meclizine; and nanovectors useful in enzyme replacement therapy contain enzyme/SBECD complex coated with biomimetic membrane (e.g. albumin) and demonstrate enhanced catalytic activity, prolonged circulation time, and improved bioavailability. Fast dissolving oral formulations using electrospinning technique were also developed.

"This non-comprehensive literature may convince the formulators on SBECD's versatile advantages in various drug delivery systems and its potential for developing state-of-the-art drug formulations," says Dr. Fenyvesi.

Gattefossé USA: SEDDS Prove Effective for NCEs & Reformulating Molecules

Gattefossé offers innovative lipid excipients and personalized technical support to accelerate customers' development programs for pharmaceutical and veterinary drugs, as well as dietary supplements. Extending to oral, (trans)dermal, mucosal, and other routes of administration, its excipients have solubility-permeability- and overall bioavailability-enhancing properties. By type of application, the product list includes self-emulsifying vehicles, solubilizers, drug release rate modifiers (sustained vs. immediate), ready-to-use vehicles for soft gelatin capsules, and emulsifying bases for topical emulsions. These excipients bring benefits to drugs by improving bioavailability, easing manufacturing, and enhancing patient compliance through taste masking, creating sustained-release matrices, and improving the texture of topical products, says Inayet Ellis, PhD, Scientific Affairs Director, Gattefossé USA.

Employing a formulation approach that can be carried from early development to marketing approval can implicate significant savings in time and costs for the overall development of new chemical entities (NCEs) that face solubility and bioavailability issues. A SEDDS formulation consisting of well-established self-emulsifying surfactants, cosurfactants, and oily vehicles can carry the development of an NCE from early preclinical to the late-stage phases. Contributing to the speed of development are also the extensive regulatory, safety, quality, and stability data provided by Gattefossé.

Reformulating drug molecules for chronic diseases is exemplified by the use of SEDDS as an effective strategy for oral delivery in testosterone replacement therapy, explains Dr. Ellis. "Traditionally, oral delivery of testosterone was unsuccessful due to extensive first-pass metabolism in the liver," she says. "However, recent FDA approvals of oral capsules formulated with SEDDS have changed this landscape. Lipids in this formulation enhance intestinal permeation and lymphatic uptake, leading to a decrease in first-pass hepatic metabolism of testosterone undecanoate, thereby maintaining its serum levels for optimum pharmacological response. Furthermore, the formulation facilitates absorption of testosterone without the necessity of maintaining a high-fat diet."

Gattefossé collaborates with pharmaceutical clients to advance their developmental programs. Recently, a client with a first-in-class, oral small molecule in oncology, developed a SEDDS formulation that facilitated the transition of the NCE from preclinical to first-in-human studies. With modified-release excipients such as Compritol® 888 ATO (glyceryl dibehenate), a cost-effective formulation has been developed to extend the half-life of an API indicated for Type-2 diabetes, she says.

Nexterone transforms amiodarone IV into a ready-to-use product for every situation (Ligand).

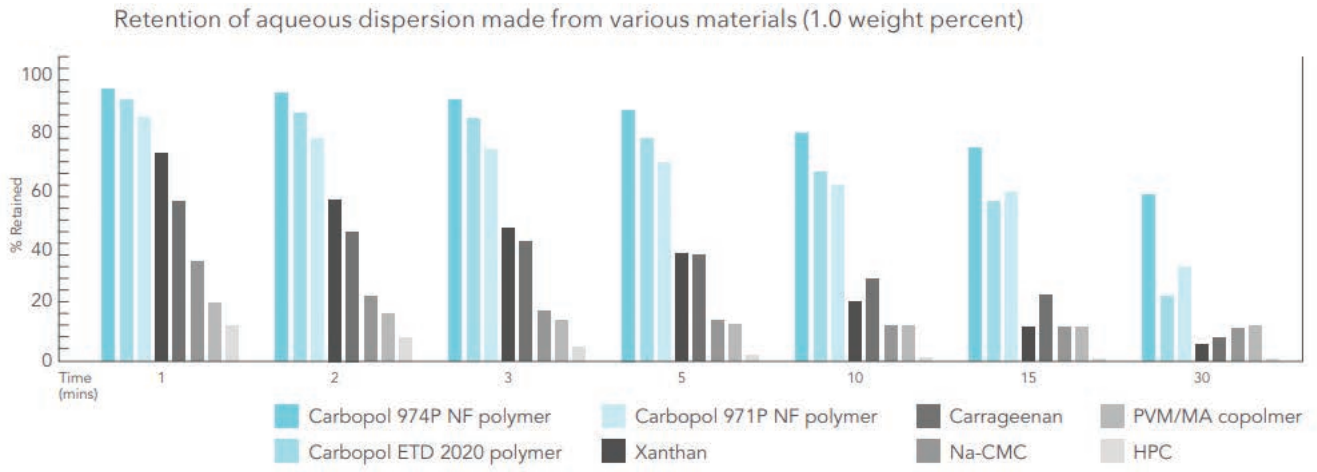
Ligand: Cyclodextrin Addresses Solubility & More

Captisol® is a uniquely derivatized beta cyclodextrin that has been in FDA-approved pharmaceutical products since 2002. The sulfobutyl ether groups of Captisol help to improve the parent beta cyclodextrin molecule's solubility, safety, and interaction with hydrophobic drug molecules, says Vince Antle, PhD, Senior Vice President, QA & Technical Operations, Ligand. "These properties, in addition to fundamental host-guest beta cyclodextrin properties, are key to the ability of Captisol to improve the solubility and stability of many different types of compounds." There are currently 16 approved products that include Captisol (SBECD) in the drug product formulation.

Because cyclodextrins are eliminated by glomerular filtration, safety questions have arisen for the use of cyclodextrins in renally compromised patients. Recent clinical studies with formulations including Captisol have shown that even in renally compromised patients, Captisol is safe to administer, says James Pipkin, PhD, Vice President, New Product Development, at Ligand. These studies have supported broad labelling for two Captisol-enabled formulations – Baxdela® (delafloxacin meglumine) and Veklury® (remdesivir) – that include renally impaired patients. Also noteworthy, the patient population for receiving Veklury has recently been expanded to pediatric patients as young as birth and weighing 1.5kg.

A benefit of using Captisol for improving solubility and stability is that the resulting formulation is aqueous-based, thereby avoiding co-solvents, surfactants, and other solubilizers that can cause their own set of safety issues, explains Dr. Pipkin. For example, amiodarone IV formulations can contain inactive ingredients benzyl alcohol and polysorbate 80 that have been shown to cause hemodynamic effects, fatal gasping syndrome in neonates, and increased hypotension,[6,7,8] while the Captisol-enabled formulation, Nexterone®, is available in a ready-to-use or Nexterone Premixed Injection. In addition to removal of excipients that affect blood pressure, added benefits of having an all-aqueous formulation resulted in a consistent droplet size during dose administration that was not regularly achieved with amiodarone formulations containing cosolvents and surfactants and decreased drug adsorption into administration infusion sets. Furthermore, the Nexterone formulations are ready to use immediately in life-saving emergencies and prevent dose inaccuracies, says Lian Rajewski, PhD, Senior Investigator at Ligand.

While stability and solubility in aqueous environment are the main reasons formulators gravitate toward adding cyclodextrins to their formulations, there are other properties of Captisol that can be exploited. For instance, Captisol is preservative-sparing[9,10] and has physical characteristics such as flow and compressiblity that are amenable to solid oral dosage forms. The Mekinist® (trametinib) oral solution formulation is a good illustration of these properties as multiple solubilizers and stabilizers were evaluated during the development of the formulation, with Captisol selected for the final product. The inventors of the oral solution composition explain:[11] "In pediatric populations, it is often desired that drug be available as a powder for reconstitution to an oral suspension or solution. Such a powder requires an attempt to dry blend various excipients with the active substance in the hope of providing a powder blend with good flow properties and content uniformity." Captisol is spray-agglomerated



Lubrizol's Carbopol® polymers offer superior mucoadhesive performance when compared to other polymers, claims the company. Lubrizol's *in vitro* study data demonstrates that Carbopol polymers provide longer retention times on mucosa versus other polymers.

and thus possesses a larger particle size with better flow characteristics than spray-dried material.

Lubrizol Life Science: Polymer Offerings Enhance Mucoadhesion & Bioavailability

Lubrizol's historic excipient brands are Carbopol®, Pemulen™, and Noveon® polymers, which serve primarily as rheology modifiers for semisolids and liquids, and extended-release polymers for oral tablets. "These bring a multitude of benefits to formulations, ranging from increased efficacy to better patient acceptance and easier processing," says Ashley Rezak, Global Market Manager, Topical Drug Delivery, Lubrizol Life Science.

Lubrizol also has Apisolex™ and Apinovex™ polymers designed to enhance the solubility of BCS Class II and IV drugs for injectable and oral applications, respectively.

Drug product development is an expensive endeavor, and while excipients make up just a portion of that cost, they can still have a critical impact on the bottom line. One method for keeping costs down is by using highly efficient excipients, such as Carbopol® polymers, says Ms. Rezak. "Only a small amount is needed to achieve high performance. For example, only 0.6% Carbopol polymer is needed versus 6% xanthan gum to achieve a similar viscosity, and the Carbopol polymer formulation offers superior clarity and suspension at this concentration."

It is known that even well-established excipients can produce negative side effects in patients, such as with polyethylene glycol (PEG), which is known to induce an immune response in some patients. This highlights the need for safe, non-toxic, and non-immunogenic alternatives to excipients such as PEG, leading to the use of PEG-based alternatives that mimic the technical properties of PEG but carry significantly lower toxicity and immunogenicity potential. Nick DiFranco, MEM, Global Market Manager, Novel Pharmaceutical Technologies, says Lubrizol's Apisolex™ polymer is being developed by Lubrizol as a polyamino acid-based technology that utilizes natural building blocks of sarcosine and other amino acids to create a safe, effective solubility enhancement option. "By promoting this technology, Lubrizol is encouraging the pharmaceutical industry to try safer, more patient-friendly options when solubilizing challenging compounds," he says.

Mucoadhesion, the adherence of two materials at least one of which is a mucosal surface, is a growing area in drug development. However, it can be difficult for a formulator to know how to instill into a formulation. A lesser-known quality of Lubrizol excipients is their ability to offer superior mucoadhesive performance compared to other polymers, which has numerous advantages such as enhanced bioavailability of a drug and lubrication of mucosal tissues.

Ms. Rezak explains: "Several clients have come to us struggling to retain an active on a target mucosal surface long enough for the drug to be effective; one example would be an eye drop or a lozenge for a sore throat, both of which struggle to remain at the site of action due to saliva or tear wash off and gravity. However, after formulating with Carbopol or Noveon polymers, their formulations achieved the desired performance and eventually made it to market."

Roquette: The Value of Starch-Based Excipients

At Roquette, everything starts with starch. Native starches can be used on their own, but, when processed, they become modified starches. Processing modified starch further produces polyols, like mannitol, sorbitol and xylitol, which can then be processed into cyclodextrins, such as hydroxypropyl beta cyclodextrin (HPβCD), for use in biopharmaceutical drug development.

"The real value of starch-based pharmaceutical excipients is in their versatility as filler/binder solutions," says Ketaki Patwardhan, Global Technical Developer, Roquette.

One dosage form benefitting from starch-based excipients is mini tablets (multiple unit dosage forms <3.0mm in diameter). These are increasingly popular in pediatric medicine. To formulate mini pills that can replace conventionally sized tablets requires the use of a highly compressible excipient, capable of producing smaller, harder tablets with the same API concentration.

"We set out to test the capacity of our PEARLITOL® 200 GT mannitol to produce melatonin mini tablets via direct compression, which could be used as one-to-one substitutes for conventional size tablets, adapted for pediatric patients," says Dr. Patwardhan.

A series of 15mg mini tablets were produced using a blend of PEARLITOL 200 GT, 3mg of the active melatonin and magnesium stearate as a lubricant, with some of the pills also featuring GLYCOLYS® sodium starch glycolate as an additional disintegrant. Each batch was subjected to different compression forces to evaluate the ideal processing parameters for mini pills.

Roquette's PEARLITOL 200 GT boosts production speeds without resulting in capped tablets.

During tablet processing, PEARLITOL 200 GT displayed excellent flowability and compressibility, enabling the production of mini tablets with minimal weight variation and capping risk, she explains. Test batches formulated without an additional disintegrant returned disintegration times of around 2-3 minutes at all compression forces upon testing, with approximately 100% melatonin dissolved in 30 minutes and more than 80% within 10 minutes. The mini tablets formulated with disintegrant showed a similar dissolution profile as the regular-sized control tablets, releasing more than 80% of the active drug within 5 minutes.

In addition to pediatric patients, Roquette services the growing demand for convenient and effective medications for an aging population, leading drug producers to search for strategies to increase tableting speed and boost output. Faster production lines often come at the expense of more frequent tableting defects and costly active ingredient waste, however. At high speeds, pockets of air can become trapped inside the tablet, leading to capping or breakage. The choice of excipient, therefore, has a significant role to play in mitigating tablet capping and assuring the quality and stability of the final drug.

"Recognizing the need to help manufacturers reduce tableting defects, we began to consider the features they would look for in a specialized anti-capping excipient," says Dr. Patwardhan. "We concluded that such a solution should be densified to allow for higher compression forces and harder tablets that are more resistant to capping, as well as having a more homogenous mass flow for faster, more efficient processing. We put these learnings to practical use in the development of our mannitol grade PEARLITOL 200 GT, which has been shown to help manufacturers boost production speeds without the typical spike in capped tablets." ◆

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ARTIFICIAL INTELLIGENCE

Embracing AI Requires Digital Literacy. How Will Your Organization Prepare?

By: Dave Watrous

INTRODUCTION

Artificial intelligence (AI) and machine learning (ML) present incredible business opportunities. But it's not enough to say, "Our business will prioritize AI."

Often, a big gap exists between the technical expertise of scientific leaders on the one hand and the strategic expertise of business leaders on the other. These groups do not always speak the same language — they either do not understand the technical capabilities and limitations of new tools or they do not see how tools might effectively change the business. To be effective, both scientists and business leaders need a strong grounding in how data science can serve their goals.

Some big pharmaceutical companies have already recognized these challenges and instigated programs to support internal digital literacy around AI and ML. As these tools become more accessible for many organizations, it is time to embark on a learning and training journey.

Perhaps your organization already has exceptional processes in place around innovation, change management, and ongoing skill development. If not, building digital literacy around ML and AI is also a great opportunity to strengthen your training strategy.

The most crucial step in building an effective plan is to figure out who needs to know what, and when. Sure, training end-users is important — eventually. First, though, decision-makers need a clear understanding of the opportunities to set goals and priorities. Then, implementation leaders need enough information to vet tools and communicate their vision.

A strong training roadmap for digital literacy begins at the top, and it begins far in advance of any major AI or ML project rollouts.

DECISION-MAKERS

When the race is on, it can feel tempting to jump in and start making decisions. But to be effective, leaders need to be humble about what they know and don't know. Ask: "Do I know enough yet to triage and prioritize where in my business this is going to make an impact?" And "Do I know enough to build teams around the most promising opportunities?" For most leadership teams, it's time to skill up. Business leaders and technical stakeholders do not need PhDs in data science. But they do have to know enough to create logical priorities about where to invest first. Then, they need to bring their teams along with them. When preparing an organization to embrace AI, leaders should start with a few key considerations.

First, they should learn the broad strokes of what AI can and cannot do. Models are, simply put, prediction machines. Machine learning models and other tools can make predictions just as well as — and sometimes better than — humans, potentially leading to huge time savings. But while models predict, they do not promise; we can't easily validate or regulate the information they produce. Human decision-making is still vital. Prediction Machines: The Simple Economics of Artificial Intelligence is one good introduction; MIT, Harvard, Carnegie Mellon, and other academic institutions also offer AI intensives for business leaders.[1,2]

To make AI useful in a pharmaceutical context, business leaders also need to understand the decisions their teams make

every day, along with the information currently used to make those decisions. Would it help to make the same decisions, but cheaper and faster? Or is it more important to aim for better decisions, using data that teams can't currently process? Opportunities and goals will vary across the drug discovery process. Pockets of the business are low risk, high reward: ML can have obvious wins for R&D and discovery. But because AI predictions are not traceable, the opportunities and risks are still not clear in more regulated stages of the biopharmaceutical lifecycle, like clinical trials and drug production.

In addition to identifying opportunities, leaders must also learn about the state of their data.[3] To be useful, AI requires good data hygiene. With incorrect information, the wrong amount of information, or even the right information organized poorly, models will make bad predictions. AI models must be trained on experimental failures as well as successes; they also need well-labeled data in which the experimental context is clear and accessible. Frank Nestle, the Global Head of Research and Chief Scientific Officer of Sanofi made this point in a fireside chat at the BIO conference last June.[4] He gave a 45-minute talk about all the amazing advances from AI in pharma. But at the end of his talk, he pointed out the key challenge: that AI won't work nearly as well as it should until companies make deep investments in structured data. A major challenge today is that early adopters want to jump in and grab a tool and play with it. But to be successful, you must understand your organization's data needs — and, likely, build serious infrastructure to make your data usable.

To assess opportunities and roadblocks, leaders need to do deep internal learning. Bring together the pockets of knowledge that already exist: Create a forum for your thought leaders to surface insights and help you develop guardrails. Pull in data science teams, IT business partners, and engineering organizations; get them talking with folks from Quality Assurance and Regulatory Affairs. Learning is collaborative: work together to identify how to strategically align your business for the opportunities and how to choose which opportunities will have the best return.

IMPLEMENTATION LEADERS

Many of the voices giving input into AI strategy will also be the people responsible for implementing the strategic decisions that come out of that initial learning journey. Once business leaders set a direction, implementation-level decision-makers will need to choose the right tools, vendors, and approaches to move the business forward. Many of these decision-makers will not be data scientists. They will also need to skill up — but maybe not quite as much as you might think. A biologist does not need to get a PhD in data science to weigh in on which tools might be the best fit for their part of the business.

For most companies, it makes much more sense to buy AI and data tools than to build them from scratch. Because AI is new and different, there is always the pressure to build internally if the right tool is not yet on the market. But this can involve regulatory risk and huge overheads.

We are at the beginning of a renaissance of low-code and no-code AI tools, as an evolving ecosystem of industry and academic collaborators bring new data science solutions to market. Unless the goal is to become an AI company first, the next step is usually to find the right partners to support your internal journey.

Tool-level decision-makers do not need the skills to build models in-house; they just need the skills to tell good from

bad. It's like driving a car. New drivers need to know the rules of the road. They also need to know enough to say, "That seems like a bad noise; probably time to take the car to the shop." But they don't need to know how to change the tires or change the oil. They don't need to know how to build and design a car — just that it would be better to drive than to walk.

Likewise, people responsible for vetting new tools need to learn about the ecosystem of viable options, the problems their teams need to solve, and the state of their data. Hopefully, they have been at the table during earlier phases of the company's AI learning journey, along with executives, and have that level of clarity.

Next, they can use the buying journey to learn more deeply. Talk with academics and potential partners to understand the key players and the lay of the land. Talk with peers about what has worked well for them. Test drive possible solutions alongside internal data scientists to flag potential implementation challenges and to iterate on RFPs as needed. Build enough competence to identify good from bad and to identify the partners that will be able to unlock the desired end state first.

Executives should also see this stage as a learning opportunity — and expect changes. Perhaps this deeper dive will uncover data connections that need to be built or goals that may need to be adjusted due to external limitations. Seen as setbacks, these discoveries can be disappointing. Seen as learning opportunities, they are a chance to solidify strategic priorities.

END USERS

Finally, once an initial ecosystem of homegrown and external tools has been identified, the next step is to train end users. At this stage, vendors will be a key resource. A vendor with experience successfully supporting organizations through digital maturity should be an excellent collaborator. Vendors can help set up architectures, think through user needs, and provide training resources for leveraging tools effectively. Interactive classroom training, on-demand training, train-the-trainer models, and custom solutions can all be part of the mix — both during the adoption phase and on an ongoing basis. A good partner will help scaffold learning, from initial change management to compliance training for core functionalities that are baked into your company's regular training process.

But the most important step in end-user training is making sure end users understand the "why." The biggest pitfall when implementing a new tool is often understanding the business case for that tool at the level of the user. End users need to be stakeholders; implementation by fiat will not support adoption.

Instead, embed the bigger vision and the potential business impact at every step in your change management roadmap, so that users who are being asked to make challenging changes can do so with a sense of purpose. Good external partners can help with this process by sharing examples of success stories that align with your goals. At IDBS, for example, we work closely with customers globally to support their data journeys, enabling more effective AI/ML investments. Through these interactions, we have learned how critical business, IT, and scientific stakeholder engagement is to overall project success.

Involve representative end users early in the company's AI learning process. When employees are bought into why the outcomes of a new tool or new data hygiene process are crucial, it can make it easier to value things that don't benefit their work directly.

The person using the tool isn't always the person who realizes the value of that tool. Still, during and after the rollout, be genuinely open to end-user feedback. Ask: Where do we need to apply innovation? What do we need to change with partners? When end users simply need to do something unpleasant, are there ways to make it less onerous? How can users be supported and celebrated for the impact of their efforts?

Leaders shouldn't opt out of learning once vendor contracts are signed. Instead, learn what's working and what can be improved. To the extent that new tools may cause changes to the organizational chart, create training pathways for new roles.

SUMMARY

There is no magic course you can take on how to conquer the pharmaceutical industry with AI: It doesn't exist because nobody's done it yet. That means "How should we train our people?" is not really the right question. Instead, it is better to ask, "How can we continue to learn and improve together?"

It can be instructive to think back to the transformations in automation that were occurring 20 years ago. Today, it is easy to find training on how to use liquid handling in your lab or which methods are best in class and why. But 20 years ago, those training courses did not exist. That's

where we are with AI and ML today.

Bring together the right people internally and the right partners externally — and make continuous learning an organizational identity — and perhaps your company will be the case study of the future.◆

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BIOGRAPHY

Dave Watrous is VP, Customer Success at IDBS and brings over 20 years of experience in leading teams in the CDMO, CRO, and Life Science markets. Before IDBS, he held roles in BioPharma companies including Covance and Cytiva. He has an academic background in the life sciences, with a BSc in Genetics, Cell Biology & Development, and another in Biochemistry, both from the University of Minnesota. He then pursued graduate studies in Cancer Biology at the University of Wisconsin.

PERSONALIZED MEDICINE

Exploring the Potential of the Aryl Hydrocarbon Receptor for Personalized Medicine

By: Pedro Moura Alves, PhD

INTRODUCTION

Personalized medicine approaches hold much promise as the future standard of care, and the aryl hydrocarbon receptor (AhR) is gaining traction as a tool for customizing therapies for both cancers and infectious diseases. Recent scientific findings have highlighted the significance of this transcription factor in immune regulation, tumor development, and therapy response. However, a comprehensive understanding of the AhR's drug response is necessary to develop tailored therapeutics. The following article emphasizes the intricacies of AhR immune sensing and signaling, and its potential for personalized treatment strategies to optimize therapeutic outcomes and minimize adverse effects. It will also touch on some of the limitations hindering the advancement of knowledge in this crucial area of research, and the direction this emerging field may take in the coming years.

UNVEILING THE FUNCTION OF THE AHR

A complex interplay of numerous factors – such as the environment, microbiota, infection, diet, stress, and metabolism – affect our health and response to disease. The body's cells are continually exposed to both external and internal stimuli, and so must be able to adapt quickly to maintain homeostasis. Multiple cellular sensors have been shown to respond to changes in the cellular microenvironment, including the AhR, a protein that has long intrigued immunologists due to its diverse roles in immune regulation. The AhR is a ligand-activated transcription factor able to detect a wide range of molecular cues, such as those originating from the environment, diet, disease, and drugs. It translates this information into highly specific cellular responses tailored to each ligand, cell, and tissue type, eliciting the actions necessary for the maintenance of homeostasis.

Notably, the AhR has been reported to be a convergence point for several signaling pathways inside the cell, including those regulating inflammation, immunity, cell proliferation and differentiation, cell morphology, cell adhesion, and cell migration. As a result, its activities are known to be implicated in the body's responses to a range of inflammatory disorders, microbial infection, and cancer. Interestingly, the receptor acts as a sensor for a variety of disease mechanisms and modulates the way the body processes and reacts to therapeutic drugs, indicating it may have a profound impact on treatment efficacy. It is hoped that, by fine-tuning the AhR's activity, the mechanism of action of many therapeutics can be improved, potentially enabling personalized medicine and enhancing treatment success for a wide range of health conditions.

ADDRESSING A WIDE KNOWLEDGE GAP

Current understanding of the molecular mechanisms and pathways involved in these AhR-drug interactions is still incomplete, sparking researchers at the Institute for Research and Innovation in Health (i3S) in Porto, Portugal, to explore this promising receptor further. The institute's Immune Sensing and Signaling Dynamics Group is dedicated to unraveling the complex intracellular network of pattern recognition receptors (PRRs) and signaling pathways triggered in different cell microenviron-

ments as part of the human body's immune response. It also investigates how this network affects, and is itself impacted by, AhR-elicited responses.

The group is dissecting AhR's complicated feedback loop to better understand how it senses and shapes the microenvironment, and how it modulates different cellular and tissue responses. The team aims to assess how AhR modulation impacts therapy efficacy, with the ultimate goal of establishing the potential of AhR manipulation in personalizing treatments for cancers and bacterial infections. The group's research therefore focuses primarily on three main areas: host-pathogen interactions, host-tumor interactions, and host-drug interactions, with mice and zebrafish being the initial model systems of choice for this exciting work.

OVERCOMING HURDLES TO DISCOVERY

The Immune Sensing and Signaling Dynamics Group's work includes screening panels of drugs that have already been clinically approved for other disease indications. On a typical day, each person within the group will process six or seven cell culture plates, changing the media in each plate several times a week. This involves the painstaking removal of excess liquid from each individual well without disturbing the cells, which is extremely time consuming and error prone. Although vacuum aspiration systems are available to aid this task, many of these instruments do not have adjustable speed settings, and so aspirate too quickly by default. This means the precious cells are often disturbed – or entirely removed from the wells along with the waste liquids – negating the team's hard work and significant time investment, as well as affecting the reliability of results and hindering the group's productivity. On top of these challenges, inconsistent pipetting of samples into wells has historically affected the accuracy and reproducibility of the team's end results, further frustrating the lab's progress and leading to repeat testing, taking up valuable additional lab time and resources.

These workflow challenges motivated the lab to search for alternative labware solutions. The team chose a VACUSAFE aspiration system and PIPETBOY pipette controller from INTEGRA Biosciences to help solve these common aspirating and pipetting issues and streamline its cell culture workflows. The VACUSAFE is renowned for its precision and efficiency and has contributed significantly to the group's ability to maintain optimal experimental conditions, which is essential for many of the lab's reporter systems. The device allows users to easily regulate the speed of aspiration for the gentle handling of fragile cell cultures. It also enables them to simultaneously and precisely aspirate liquid from eight wells at a time, rather

than one by one, saving valuable hands-on time and reducing the likelihood of incurring the repetitive strain injuries frequently associated with heavy liquid handling workloads.

The PIPETBOY provides users with a high level of control over liquid levels during serological pipetting, and the team uses this superior control to streamline the dispensing of cells and exchange of media between different labware formats across various aspects of their workflows. This has noticeably enhanced the speed, accuracy, and reproducibility of all the lab's complicated pipetting tasks, contributing to improving the quality of their research outcomes.

SUMMARY

The new knowledge gained from studying the role of the AhR in immune sensing and signaling dynamics will certainly play a key role in the development of novel personalized therapeutic strategies for both infectious diseases and cancers in the future, and already holds much promise for improving patient outcomes through custom treatment solutions. Although still in early days, the cutting-edge AhR research being carried out by the Immune Sensing and Signaling Dynamics Group at i3S may prove to be a foundation for bridging the gap between fundamental immunology research and clinical applications and could ultimately help to accelerate the field of personalized medicine. ◆

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

BIOGRAPHY

Dr. Pedro Moura Alves has been Group Leader of the Immune Sensing and Signaling Dynamics Group at i3S since February 2022. He studied Biochemistry at Universidade da Beira Interior, Portugal, graduating in 2004, and moved to Boston, MA in 2005 to embark upon a PhD within the group of Prof. Bruce Walker. He returned to Portugal in 2007 and joined the group of Dr. Luís Ferreira Moita, finishing his PhD in 2010, and then became a post-doctoral fellow at the Max Planck Institute for Infection Biology. In March 2019, he started his independent research group at the Ludwig Institute for Cancer Research, University of Oxford, UK.

DRUG DISCOVERY

Addressing Challenges in Drug Discovery: DEL Screening Applications

By: Matt Clark, PhD

INTRODUCTION

DNA-encoded library (DEL) screening has emerged as a well-established technique in early stage drug discovery. Many large pharmaceutical companies (and a handful of service providers) operate DEL platforms, and the number of published DEL successes is growing year over year.

One reason for DEL's growing popularity is the fact it is well-suited for solving key problems in contemporary drug discovery. The following will explore DEL's application in three areas of drug discovery that have received much attention throughout the past 5 years: Induced Proximity, Covalent Drug Discovery, and Machine Learning.

INDUCED PROXIMITY

The use of small molecules to induce the proximity of protein pairs represents a revolutionary new modality in drug discovery. This approach allows researchers to harness cellular machinery to modulate protein (or RNA) functions, effectively mitigating disease. The first example of induced proximity to gain attention is Targeted Protein Degradation (TPD).[1] In TPD, the goal is to induce proximity between a disease-causative protein (often referred to as a Protein of Interest or POI) and an E3 ligase. By doing so, the POI is drawn into the E3's associated ubiquitinylation machinery and thereby labeled for proteasomal destruction. As such, TPD does more than just inhibit disease-associated POIs; it eliminates them altogether.

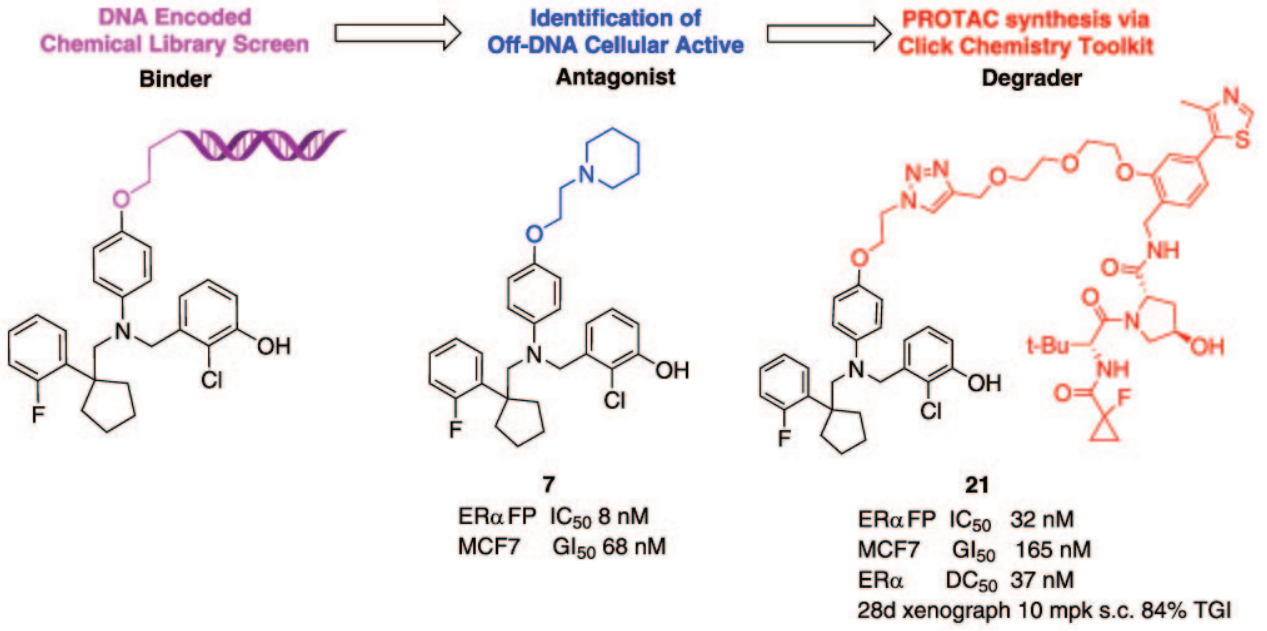
To induce proximity between these proteins with a small molecule, the molecule must have binding affinity for both proteins. This is commonly achieved by creating so-called "chimerical" compounds, in which binding moieties for both the E3 and the POI are connected by a chemical linker. This modular approach simplifies the design of TPD agents. Binders for E3s are documented in the literature, centering the main workflow on discovering POI binders, linking them with known E3 ligands, and optimizing for degradation efficiency and ADME. It is within this workflow that DEL really shines.

At its heart, DEL screening is a binding experiment. Compounds displaying affinity for the POI are isolated from the bulk library and identified through DNA sequencing. Because TPD requires only affinity (not functional effects like inhibition), DEL hits can be seamlessly integrated into a chimeric molecule and assessed for degradation ability. An efficient workflow can be implemented wherein DEL hits are re-synthesized off-DNA with a reactive linker in place of the DNA attachment. These hits can then be coupled with commercially available E3 ligands featuring complementary reactive handles. This facilitates swift array synthesis, enabling the generation of tens or even hundreds of candidate degraders that explore diverse combinations of E3 ligands, POI binders, and linkers. These candidate degraders can be directly tested for their protein knockdown effects.

A publication describing this workflow appeared in 2020 (Figure 1).[2] Ligands for the oncology target estrogen receptor α (Erα) were discovered by DEL screening, resynthesized with reactive linkers, and linked to E3 ligands. It was quickly determined that the E3 VHL was the optimal partner in this system, and the first tested compound was shown to degrade Erα with a potency of 38 nM.

Induced proximity approaches extend beyond just TPD. Newer modalities, such as AUTACs, RIBOTACs, DUBTACs, and many others rely on different cellular mechanisms, such as autophagy or RNA degradation. These approaches expand the toolkit of induced proximity through targeting RNA, extending the lifetime of proteins, or degrading proteins by non-E3-dependent

FIGURE 1



From on-DNA hit to protein degrader.[2]

mechanisms. But in all cases, high-quality, linkable ligands will be required, making DEL a powerful enabling technology as these modalities mature.

A new frontier in induced proximity is the emergence of molecular glues, non-chimerical compounds that can induce protein interactions. Glues could have significant advantages over the modalities previously discussed because they should have better developability properties than chimerical compounds (eg, lower molecular weight, fewer rotatable bonds, improved metabolic stability). The search for novel glues is daunting; rather than finding the proverbial needle in the haystack, glue discovery is like searching a mountain of haystacks. Fortunately, the size and scope of DEL libraries indicate that the direct discovery of glues should be possible. DEL glue selection proof-of-concept experiments are ongoing at several labs and reports are on the horizon.

COVALENT DRUG DISCOVERY

Another emerging (or re-emerging) modality that DEL will accelerate is covalent drug discovery. These drugs form covalent associations with their biological targets — typically proteins via their reactive amino acid side chains (eg, cysteine). The bonds are typically irreversible, meaning the drug compound becomes permanently bound to the target. This approach has obvious advantages in terms of potency, duration of action, and pharmacokinetics. But despite these advantages, covalent drug discovery attracted little attention for many years. This reluctance was based on the perception that covalent drugs had a higher risk of off-target activity and toxicity than conventional drugs (it should be noted that aspirin is a covalent drug).

Covalent drug discovery has generated renewed interest in recent years. For example, in the early 2010s, several companies brought cysteine-targeted covalent kinase inhibitors to market. Additionally, chemoproteomics researchers showed that the reactivity of protein side chains could vary widely based on the local environment, supporting the possibility of selective targeting. Lastly, new reactive groups were introduced that went beyond cysteine-targeting, making it possible to target other amino acids, such as serine and lysine.

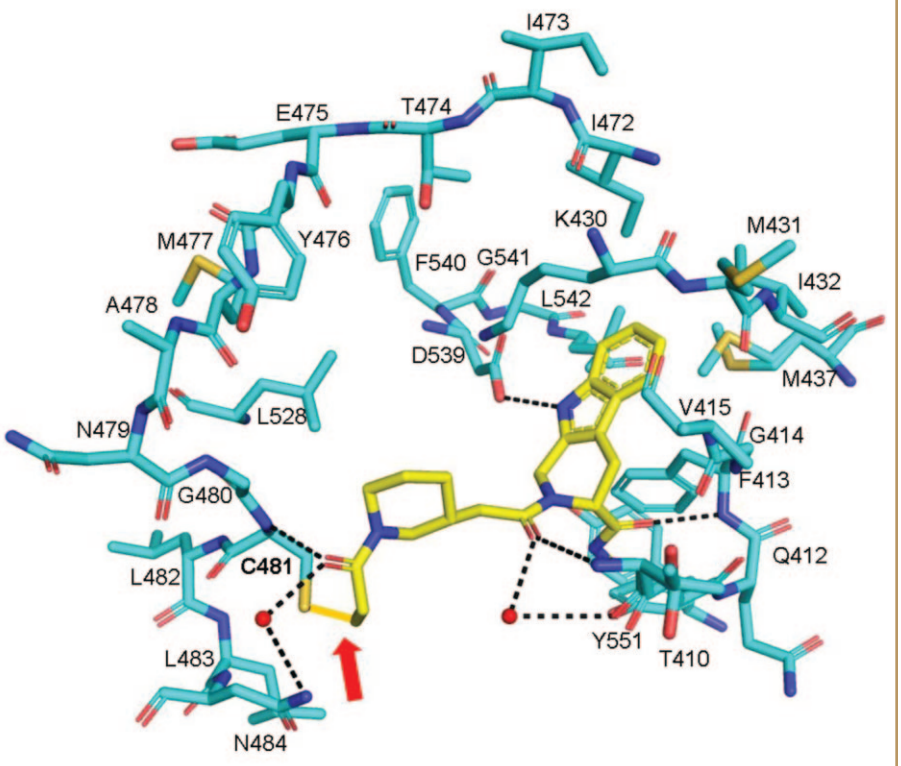
With this renewed interest, the question then arose: how to best discover covalent drugs? Screening large collections of reactive compounds appears to be impractical because of the likelihood of limited shelf-stability (compared to non-reactive compounds, as typically utilized in high-throughput screening). Two approaches that bypass this problem, however, have shown success. The first is the re-purposing of non-covalent compounds. In this process, researchers take a pre-existing non-covalent ligand, and using structural information about nearby side chains in the binding site, append it with a reactive group to target a specific side chain. The BTK inhibitor ibrutinib is an ex-

ample of this approach.[3] The second method is to screen small numbers of covalent fragments and elaborate the hits into suitably potent drug candidates. This process was exemplified by the discovery of KRas G12C inhibitors, all based on a small reactive fragment (discovered by professor Shokat at University of California San Francisco).[4]

DEL screening represents a new and powerful approach to covalent drug discovery. Encoded libraries containing reactive groups can be prepared just like conventional DELs. Installation of the reactive groups may be conducted immediately prior to screening to minimize storage time and possible decomposition. These reactive library members are not fragments; rather, they are fully elaborated lead-like or drug-like compounds. In the screening experiment, the library is exposed to the desired protein target, and only those compounds that are permanently attached to the protein (and survive extensive washing) are sequenced and analyzed. Because DEL analysis is based on the differential enrichment of hit compounds over other library members, reactivity-based promiscuity is addressed immediately in the screening experiment. Thus, we can see that DEL directly addresses a major challenge faced in covalent drug discovery.

One published example of covalent DEL screening illustrates these advantages.[5] The kinase BTK was screened using DELs that contained several different reactive groups. The resulting hits were structurally unrelated to any known noncovalent BTK inhibitors, although they did share a substructure with the DEL-derived BTK ligand reported earlier by the same group (Figure 2). Furthermore, the compounds were exquisitely selective, showing once again that covalent drugs need not be promiscuous.

FIGURE 2



Structure of DEL-derived covalent inhibitor bound to BTK. Arrow shows the covalent bond.[5]

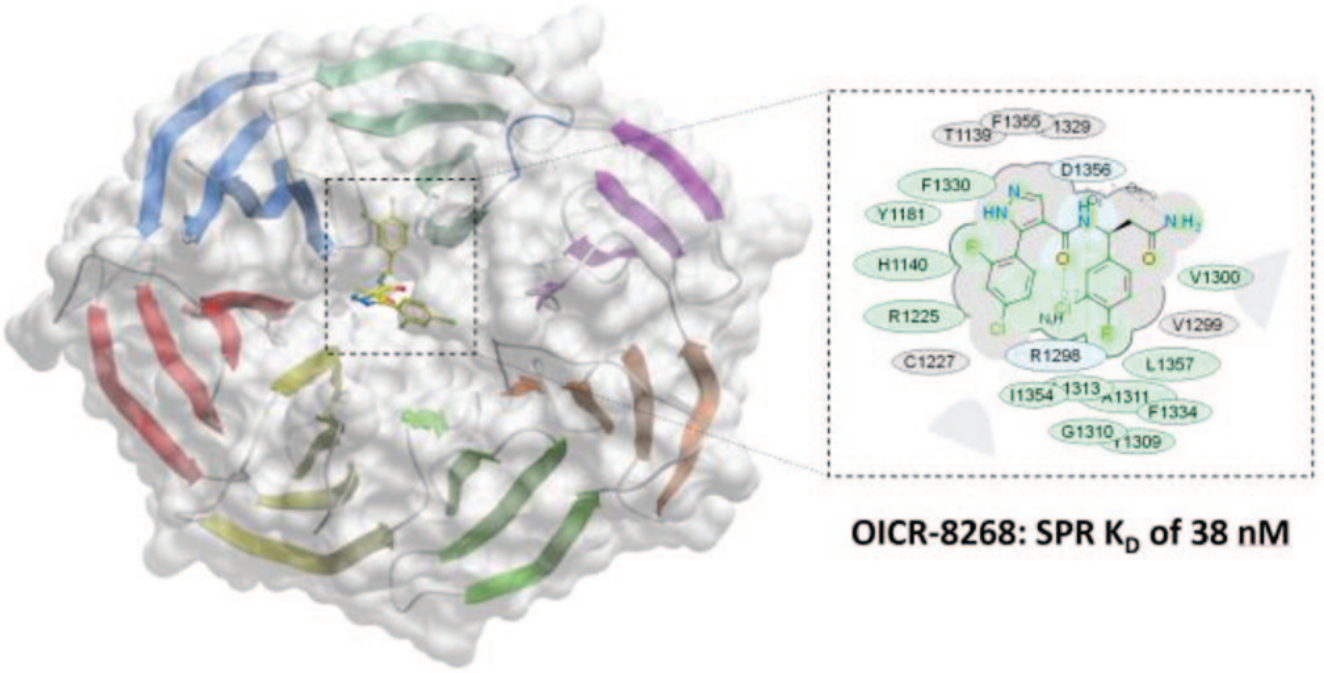
MACHINE LEARNING

The use of machine learning (ML) in drug discovery has attracted considerable interest throughout the past 5 years. ML holds the promise of taming the incredible volume and diversity of data produced by drug discovery research, yielding novel insights. Medicinal chemistry has been described as the ultimate multiparameter optimization problem, in which numerous factors like potency, stability, permeability, toxicity, solubility, and others must be honed simultaneously. ML is well-suited to addressing the multiparameter problem, thereby accelerating the discovery of new drug candidates.

There is a paradox, however, in the embrace of ML in drug discovery. The highest-value, most novel drug targets are those that have the least amount of historical data, especially chemical data. New targets emerge in the literature, indicated by proteomic or genomic data as being involved in a particular disease state. Throughout the ensuing years, as hit generation and lead optimization campaigns progress, a chemical data resource for the target gradually accumulates. This means that for the highest value targets, it can take years to decades to amass sufficient chemical data to allow ML to add value.

DEL short-circuits this problem. The DEL screening experiment relies on DNA sequencing to characterize the compound structures bound to the target. Because modern techniques can generate millions of individual sequences for a modest cost, DEL can produce millions of chemical data points very quickly. This quantity of chemical data surpasses that which can be generated by any other screening modality, and it is sufficient in scope and depth to bring ML to bear. Essentially, DEL screening rapidly generates a quantity of data

FIGURE 3



Structure of ML-derived ligand bound to DCAF1.[7]

that would take other modalities years to produce. Thus, even unprecedented targets can be swiftly enabled with a DEL screening was used to generate such a model, and one of the first known DCAF1 ligand was found in a commercial virtual library (Figure 3) data resource.

Recent peer-reviewed publications validate this proposition. In a proof-of-concept experiment reported in 2020, X-Chem and Google collaborated to apply ML to DEL datasets across a small set of pharmaceutically relevant targets.[5] The resulting ML models were adept at predicting new binders from untested virtual libraries. More recently, this method has moved beyond proof-of-concept and demonstrated successful hit generation for targets for which no binders had been previously reported. In early 2023, Li and colleagues at the University of Toronto and the Structural Genomics Consortium (SGC) demonstrated the DEL and ML workflow in action, focusing on the novel target DCAF1.[6] At the time of publication, no ligands for DCAF1 had been reported. Consequently, there was no corpus of historical data to rely on for ML model training. DEL screening was used to generate such a model, and one of the first known DCAF1 ligand was found in a commercial virtual library (Figure 3).

A second example of this workflow was recently disclosed by workers from the same institution. In this case, the target was WDR91, another novel target for which no ligands were known.[7] Once again, the DEL and ML workflow was able to generate the first known ligands for WDR91. Following from these successes, X-Chem and the SGC recently announced a collaboration aimed at bringing this technique to scale, using DEL and ML to find probes for the drug targets of the future.[8]

As this methodology continues to develop, it is likely to move beyond early adopters in academia and begin to find purchase in biotech and pharma. An important question remains about the breadth of applicability and the critical mass of libraries and screening data needed to build effective models. We eagerly anticipate the development of this field in the coming years as we tackle the difficult targets of the future.

SUMMARY

As always, new opportunities and challenges abound in drug discovery. New modalities, such as induced proximity, promise to unlock new vistas in how we attack disease. Innovations breathe new life into older techniques like covalent drug discovery. And advances in computational power allow ML to illuminate hidden patterns in vast data repositories. In all three cases, the power of DNA-encoded library screening will drive and enable these advancements to create the drugs of the future, fulfilling the unmet medical needs of patients around the world. ◆

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BIOGRAPHY

Dr. Matt Clark is a world-recognized innovator and leader in the DNA-encoded library (DEL) field. He was part of X-Chem's founding team, served as VP of chemistry, SVP of research and CEO prior to his appointment to the CSO position. Under his scientific leadership, the company developed from a niche chemical discovery platform to a world-leading drug discovery engine serving the biopharma industry. Before joining X-Chem, he was director of chemistry at GlaxoSmithKline, where he led the group responsible for design and synthesis of early-iteration DELs. He began his professional career at Praecis Pharmaceuticals, where he played a key role in the early development and implementation of technologies that would become the basis for DEL. He is a thought leader in the DEL space, with numerous patents and key DEL publications to his name. He earned his B.S. in biochemistry from the University of California, San Diego, his Ph.D. in chemistry from Cornell University and conducted post-doctoral studies at the Massachusetts Institute of Technology.

THERAPEUTIC FOCUS

Sarilumab Approval for Polymyalgia Rheumatica Highlights Enduring Unmet Medical Needs

By: David A. Katz, PhD, and Robert Jacks, MBA, MSE

INTRODUCTION

An IL-6 receptor antagonist, sarilumab (Kevzara®, marketed by Sanofi/Regeneron), recently gained FDA approval for the treatment of polymyalgia rheumatica (PMR). Sarilumab is the vanguard of a few new therapies now being developed by pharmaceutical companies for PMR, a disease long overlooked by the industry despite its high prevalence and debilitating symptoms. Sarilumab's approval is beneficial for patients with PMR: a new, effective treatment option is now available, promotion of the drug will increase disease awareness, and the success encourages others in the industry to continue and expand their PMR research. However, the proportion of patients who can benefit from the drug is limited. Significant unmet needs remain for all persons suffering from PMR.

OVERCOMING THE CHALLENGES OF TREATING PMR

PMR is the most common autoimmune illness of the elderly and second only to rheumatoid arthritis in prevalence of all rheumatic diseases. Bilateral shoulder pain is the most frequent presenting symptom; hip (also usually bilateral) and neck pain, stiffness, and fatigue are also core symptoms.[1] PMR is uncommon prior to age 50, most often presenting between ages 70 and 80. PMR is about 70% more common in women compared to men. Incidence and prevalence data show a substantial decreasing cline from Northern to Southern Europe, and the disease is uncommon or rare in persons of Black or East Asian race.[2] The US prevalence, based from age-, sex-, and year-specific incidence rates and adjusted to the US White population, was estimated to be 701 [95% CI: 651-750] per 100,000, which translates to approximately 840,000 current persons with PMR in the US.[3]

PMR can be challenging to diagnose. It's not unusual that a patient receives a confirmed PMR diagnosis only after achievement of remission with a moderate glucocorticoid (steroid) dose of 12.5-25-mg prednisone equivalent daily. The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) guideline recommends a taper to 10 mg within 4-8 weeks and a 1-1.25-mg dose reduction every 4 weeks thereafter until discontinuation, provided remission is maintained.[4] The purpose of taper is to avert the various and well-established morbidities of steroid use, which can include osteoporosis, difficult-to-control diabetes and hypertension, adiposity, cardiovascular disease, glaucoma, muscle and skin atrophy, and mood, sleep, and cognition deficits. But 43% (29%-56%) of patients relapse within a year, and many are unable to taper to discontinuation – at 1, 2, and 5 years after steroid initiation, 77% (71%-83%), 51% (41%-61%), and 25% (15%-36%) remain on steroids.[5]

For 6 decades, patients with PMR have faced a Hobson's choice between the symptoms of their disease and the side effects of their medicine. Steroid side effects can be even more impactful for elderly patients – consider the probability of long-term disability associated with fracture in someone in their 70s or 80s compared to younger adults. Patients with PMR, because of their age, are also more likely to have comorbid conditions, such as diabetes, hypertension, and glaucoma that can be exacerbated by steroid use.

Until recently, patients with PMR had no third option: the only approved therapy for PMR was steroids. (Historical note: Steroids were never approved by the FDA for treatment of PMR according to modern standards. The indication preceded the Kefauver-Harris Act of 1962.) DMARDs (eg, methotrexate, leflunomide) are used as steroid-sparing agents, but their efficacy has not been demonstrated, and most patients who receive DMARDs still require steroids even if at a lower dose. Several biologics have been

tested as steroid-sparing agents, but most failed to show efficacy, for example, tumor necrosis factor blocking agents, which the EULAR/ACR guideline recommends against for the treatment of PMR.

NEW CLINICAL RESEARCH CREATES HOPE

Early signs of a new hope came from two academic clinical trials of the IL-6 receptor antagonist tocilizumab. Low or no disease activity together with a protocol-specified decrease of steroid dose in patients with active PMR was achieved in 33 of 49 treated with tocilizumab and 16 of 51 treated with placebo.[6] Glucocorticoid-free remission at week 16 in patients with new-onset PMR was achieved in 12 of 19 treated with tocilizumab and 2 of 17 who received placebo.[7] These results confirmed the pathophysiological role of IL-6 in PMR and have led to off-label prescription of tocilizumab. However, there's no sign tocilizumab, now subject to biosimilar competition, will gain an indication for PMR.

In the registrational trial for the IL-6 receptor antagonist sarilumab (NCT03600818), patients diagnosed with PMR, at a current steroid dose of 7.5- to 20-mg prednisone equivalent daily, with a history of PMR disease flare at a dose of no less than 7.5 mg, and having recent biochemical evidence of inflammation associated with PMR disease activity were randomized equally to two treatment arms:

- sarilumab injected every other week, prednisone tapered from 15 mg to discontinuation at week 14, or
- placebo for sarilumab injected every other week, prednisone tapered from 15 mg to discontinuation at week 52

The primary endpoint was the proportion of patients who achieved sustained remission at week 52 defined by achievement of four components:

- disease remission no later than week 12
- absence of disease flare from week 12 through week 52
- sustained reduction of C-reactive protein to < 10 mg/L from week 12 through week 52
- successful adherence to the defined prednisone taper from week 12 through week 52

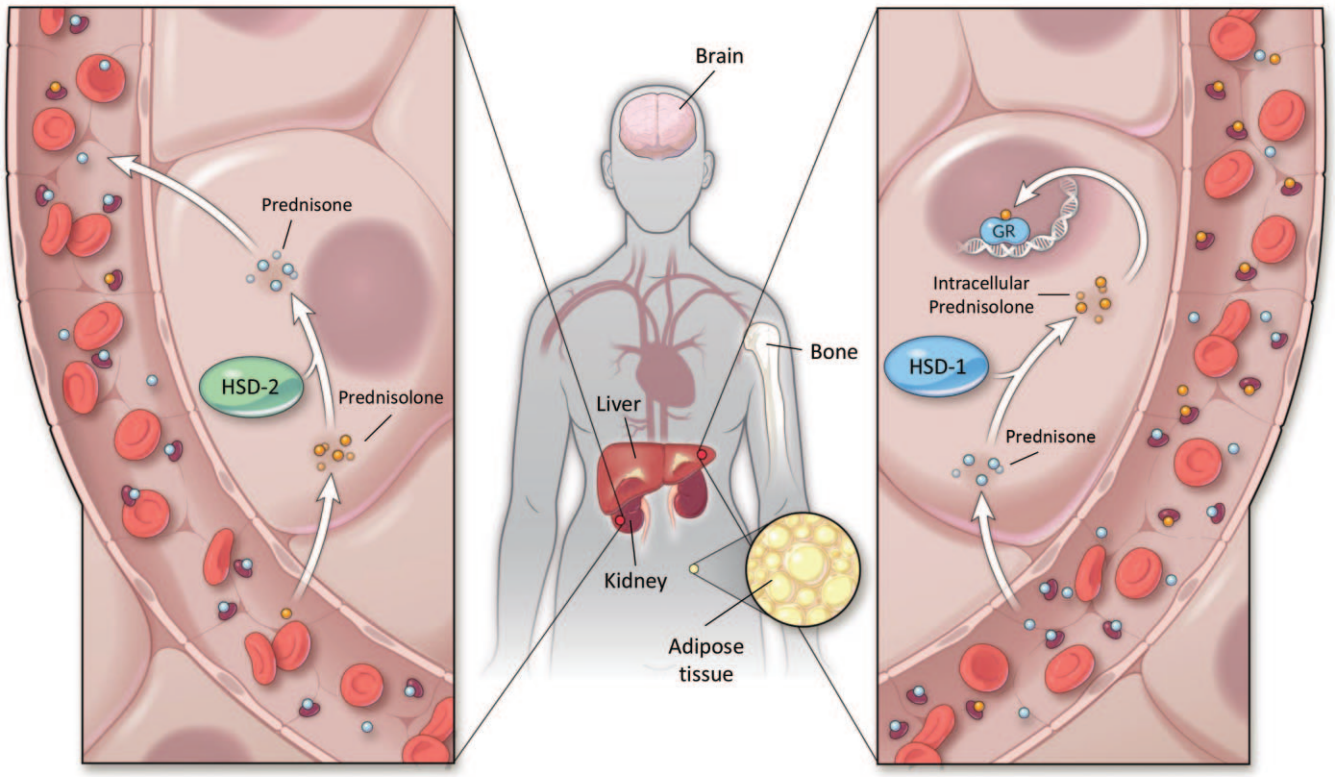
Sustained remission was achieved by 17 of 60 patients who received sarilumab and 6 of 58 who received placebo. The package insert shows sarilumab was associated with numerically higher proportions of patients who achieved each of the four components of sustained remission, as well as substantially lower cumulative steroid dose through week 52.[8]

Consistent with the trial population, sarilumab is only indicated for patients with PMR who have had an inadequate response to, or cannot tolerate, glucocorticoids (steroids). Sanofi/Regeneron market research suggests that's about one-third of patients with PMR. Sarilumab is, therefore, not indicated for the majority of patients with PMR. Furthermore, based on the clinical trial results, only about 28% of patients who try sarilumab will achieve sustained steroid-free remission. That is only approximately 18% more than what was achieved in the control arm of steroids alone, meaning sarilumab has only demonstrated additional benefit for 18% of one-third of PMR patients, or approximately 6% of all patients with PMR. Finally, sarilumab is only indicated in combination with steroids, so all treated patients continue to be exposed to steroids, which have not been shown to be free of safety risks at any dose or duration.

Sarilumab also carries a black box warning for risk of serious infections and warnings for neutropenia, thrombocytopenia, elevated liver enzymes, lipid abnormalities, and gastrointestinal perforation. It's an injectable product, which many view as less desirable than a pill. And it's expensive ($57,526 per year; caremark.com accessed June 27, 2023), which limits access. The bottom line: while sarilumab will undoubtedly help some patients with PMR, it has limited efficacy as well as safety, convenience, and cost-related challenges. Unfortunately, all patients suffering from PMR continue to have substantial unmet medical needs.

NOVEL THERAPY APPROACHES TO PMR TREATMENT

Patients with PMR might have additional novel therapy choices in the coming years, as the industry has begun to recognize the unmet needs of the large population of patients with PMR. Secukinumab (Cosentyx®, marketed by Novartis), an anti-interleukin 17A antibody currently indicated to treat plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic ankylosing spondyloarthritis, is in a Phase 3 clinical trial (NCT05767034) as a steroid-sparing agent for treatment of PMR. ABBV-154, an antibody-drug conjugate of the TNFα inhibitor adalimumab and a novel glucocorticoid receptor antagonist, had been in a Phase 2 clinical trial (NCT04972968). However, AbbVie announced in April 2023 that ABBV-154 development was discontinued due to its risk profile.[9] Others have initiated development of similar antibody-steroid conjugates with the aim of using the antibody to target the steroid to immune cells, thereby limiting systemic



HSD-1 is a Novel Therapeutic Target for PMR
Steroids such as prednisolone are the standard of care for PMR. In the body, prednisolone is inactivated in tissues such as kidney where it's acutely toxic, to prednisone which returns to circulation. Prednisone is reactivated to prednisolone by HSD-1 in many tissues, including liver, adipose, bone, and brain in which excess intracellular prednisolone can cause long-term toxicity such as diabetes, obesity, osteoporosis, and depression. HSD-1 inhibitors, co-administered with prednisolone, might ameliorate prednisolone toxicity by blocking formation of excess intracellular prednisolone.

steroid exposure.

PMR patients need a treatment that is effective, safe, convenient, and accessible. Steroid-sparing biologics, although they can be effective options for some patients, each have their own safety issues, usually still require concomitant steroid use, are not the most convenient form of drug, and collectively represent a large economic burden as the most costly drug class for all of us who pay for them through insurance premiums or taxes. Steroids are highly effective to treat PMR, to the point steroid response can be the basis for diagnosis of PMR rather than another disease with similar symptoms. Many patients who don't respond favorably to steroids probably would with a higher dose or longer duration, both of which are discouraged to protect patient safety.

Rather than another steroid-sparing agent, a novel approach is to develop a steroid side-effect-sparing agent. One company trying this approach is Sparrow Pharmaceuticals. SPI-47 is in a Phase 2 clinical trial as a fixed-dose combination of the steroid medicine prednisolone with SPI-62, an inhibitor of the intracellular enzyme 11β-hydroxysteroid dehydrogenase type 1 (HSD-1). The HSD-1 inhibitor is intended to reduce the side effects of the steroid, thereby allowing for safer treatment with the highly effective medicine.

In vivo, steroids cycle between active (eg, prednisolone) and inactive (eg, prednisone) forms. Inside cells, HSD-1 converts inactive steroids to their active form. The common steroid medicine prednisone is actually an inactive prodrug that requires HSD-1 for activation to prednisolone. What is not well appreciated is that it is the level of active steroids available intracellularly that matters most for the unintended side effects of steroids. Circulating levels of either active or inactive steroids are less consequential.

Prednisolone is inactivated to prednisone by a different enzyme, HSD-2, in tissues where steroids are acutely toxic, most prominently in the kidney. Circulating prednisone is re-activated to prednisolone intracellularly predominantly in liver and other organs such as adipose, brain, bone, skin, muscle, and eye where steroid excess can lead to known safety problems. Potent inhibitors of HSD-1 lower active intracellular steroid levels in several of those tissues, thereby potentially reducing the side effects of steroid use.

In mice, SPI-62 prevented steroid-associated hyperphagia, accelerated weight gain, insulin resistance, increased adiposity, and muscle and skin atrophy (submitted for publication). In a recent academic clinical trial, the HSD-1 inhibitor AZD4017, when given in combination with prednisolone to healthy adult males, prevented many acute toxicities of the steroid.[10] HSD-1 inhibition prevented sup-

pression of the bone formation biomarkers osteocalcin and procollagen type I N-propeptide, increase of the bone resorption biomarker C-terminal collagen type I crosslinks, reduction of insulin sensitivity and glucose disposal measured during an insulin clamp, elevation of triglycerides, and night-time diastolic hypertension. HSD-1 is also expressed at low levels in cells of the human immune system. That expression might contribute to the observations that AZD4017 prevented prednisolone effects on some immune biomarkers but not others. None of the affected biomarkers are understood as relevant to PMR pathophysiology, so the implication of those findings on the efficacy of prednisolone in patients is unclear.

The ongoing Phase 2 clinical trial of SPI-47 in patients with PMR (NCT05436652) aims to determine whether co-administration of SPI-62 can both reverse adverse prednisolone effects (eg, changes on bone biomarkers consistent with an osteoporotic phenotype) and preserve desired effects (ie, symptomatic control of PMR, suppression of cytokines and acute phase biomarkers that have been associated with PMR disease activity). If successful, this trial will provide clinical proof-of-concept for the steroid side effect-sparing approach of HSD-1 inhibition.

CONCLUSION

2023 is a banner year for patients with PMR. After a 6-decade wait, they have a new treatment option – the IL-6 receptor antagonist sarilumab. The pharmaceutical industry has awakened to their enduring unmet medical need, which even with the approval of sarilumab remains substantial. Another steroid-sparing biologic, secukinumab, with a distinct mechanism of action and already available for treatment of other rheumatic diseases, is in a Phase 3 clinical trial. Finally, a novel approach with HSD-1 inhibition has the potential to yield a medicine that shares the same efficacy and convenience as today's steroids while reducing the safety challenges that currently limit steroid utility. ◆

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BIOGRAPHIES

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Robert Jacks is Chief Executive Officer of Sparrow Pharmaceuticals and has 20 years of experience in the biopharmaceutical industry. He has founded or co-founded multiple companies and raised more than $170 million. Previously, he was the President & CEO of Indalo Therapeutics, a clinical-stage biotechnology company developing therapeutics for serious fibrotic diseases, and President, CFO, and Co-Founder of Symbiomix Therapeutics, which was sold after achieving NDA approval for Solosec®. He also previously held the positions of Head of Corporate Development for Tobira Therapeutics, Head of Business Development for ACT Biotech, and Entrepreneur-in-Residence for OrbiMed Advisors. He began his pharmaceutical industry career in finance and product development at Pfizer, where he last worked as the Director of Business Development for Oncology and Infectious Diseases. He earned an MBA from Columbia Business School, an MSE in Civil Engineering from Stanford University, and a BSE in Civil Engineering from Duke University.

CANCER BIOMARKERS

Co-Analysis of CTCs & ctDNA: Gaining Multi-Dimensional Insights Into Cancer Heterogeneity

By: Yoon-Tae Kang, PhD, Abiodun Bodunrin, PhD, and Joby Chesnick, PhD, MBA

INTRODUCTION

Despite the progress made in cancer diagnosis and treatment, metastasis remains the predominant cause of cancer-related fatalities worldwide. A significant constraint to enhancing patient outcomes lies in the limitations of current clinical diagnostic tools, which struggle to predict the progression of metastasis and detect minimal residual disease, ie, a small number of cancer cells that are often undetectable by conventional methods post-therapy. Standard-of-care (SOC) methods, which include tissue biopsies, imaging technologies, and tumor markers, often fall short in assessing comprehensively all aspects of a patient's cancer.[1] This limitation arises from diagnostic thresholds that are not robust, sampling biases associated with temporal and spatial tumor heterogeneity, and constrained access to metastatic lesions.

A promising solution emerges in the form of liquid biopsies, offering a real-time and minimally invasive avenue for early detection, prognosis, solid tumor status monitoring, and predicting responses to cancer therapy.[2] The concept of liquid biopsy based on circulating tumor cell (CTC) detection was proposed in 2011, followed by the inclusion of circulating tumor DNA (ctDNA) utilization for obtaining tumor biological information within the scope of liquid biopsy.[3,4]

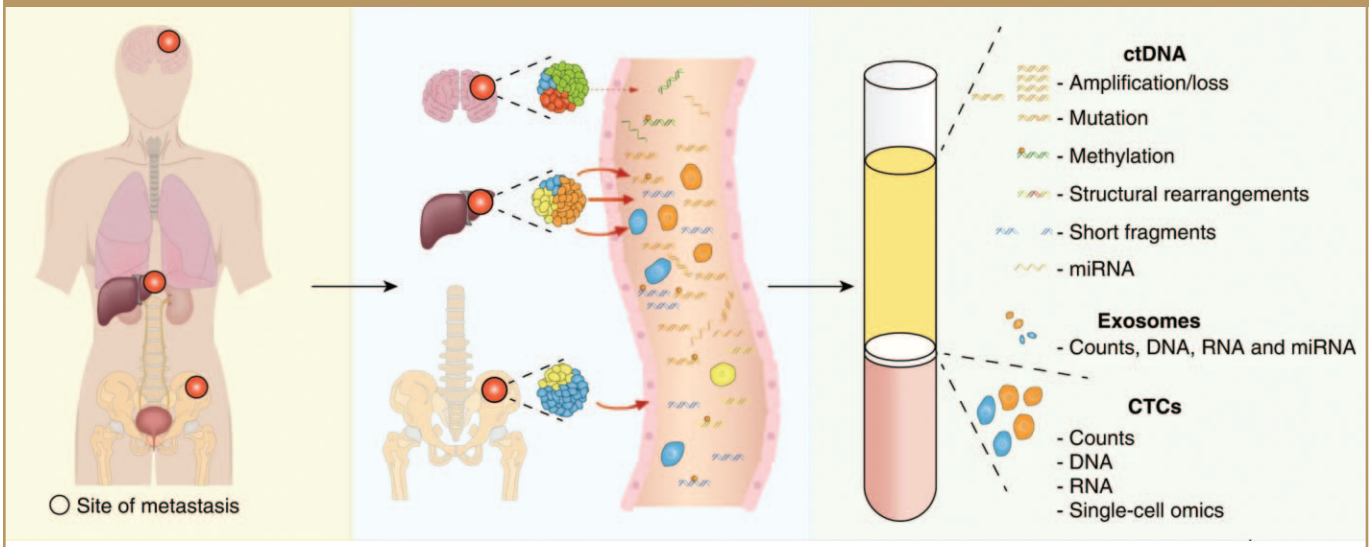
With significant translational potential, numerous clinical trials are currently leveraging CTCs and ctDNA as indicators of tumor burden and progression, each reflecting distinct biological aspects of the disease.[2] Each component presents unique advantages, with both CTCs and ctDNA providing complementary information about tumor dynamics. ctDNA, small cell-free DNA fragments (~160bp) present in liquid biopsy samples, has garnered more attention from researchers due to its ease of isolation from blood and the presence of cancer biomarkers-of-interest that have the potential to impact therapy decisions.[5] In contrast, CTCs, though typically sparce in blood samples (as few as 1 cell/mL of blood), offer a more comprehensive source of genomic, gene expression, and epigenetic gene regulation information from living intact cells. CTC analysis can provide insights into various aspects of cancer biology and other characteristics associated with metastatic behavior, including endothelial-to-mesenchymal transition (EMT) changes responsible for CTC loss of adhesion from the primary tumor and entry into the circulatory system to eventually form secondary tumors in distant organs.[6]

Co-analysis of CTC abundance and phenotypic changes together with ctDNA concentration could allow for real-time monitoring of disease progression and reoccurrence, while genetic and epigenetic changes in CTCs and ctDNA mutations over time could provide valuable insights into the effectiveness of therapeutic interventions, as the presence of different somatic mutations may indicate cancer susceptibility or resistance to certain treatments (Figure 1).[7] Such proposed dynamic monitoring could guide adjustments to treatment strategies, ensuring a more personalized approach to cancer treatment.

UNDERSTANDING THE LINK BETWEEN TUMOR HETEROGENEITY & TREATMENT EFFICACY

Cancer therapies depend, to a large extent, upon our ability to capture cancer tumor heterogeneity, ie, differences in their DNA and gene expression, which allow us to predict the tumor's susceptibility or resistance to specific drug or hormone therapies. Monitoring phenotypic, genetic, and epigenetic CTC changes,

FIGURE 1



Example of circulating tumor material originating from genetically distinct cells within individual tumors that could be isolated following liquid biopsy analysis. Adapted from Trujillo et al. 2022, under a CC BY 4.0.

and ctDNA mutations over time, could provide valuable insights into the effectiveness of therapeutic interventions. This dynamic monitoring could prove useful to guide adjustments to treatment strategies, ensuring more precise and targeted interventions.

CTCs, as a diverse cell population with distinct molecular phenotypes from primary tumors, represent an accessible and up-to-date cancer sample for real-time monitoring and detection of diagnostic biomarkers and therapeutic targets. In addition to their association with metastasis, CTCs can possess DNA mutations and unique surface markers not found in the primary tumor that can reduce the efficacy of radiation and targeted therapies tailored to the primary tumor. For example, HER2 expression on CTCs captured from breast cancer (BC) patients is often associated with unfavorable clinical outcomes and poor response to anti-HER2 therapy. This expression may represent a change in biomarker phenotype from the primary tumor from which the CTC was derived (ie, HER2 negative primary tumor).[6]

The impact of ctDNA analysis on clinical outcomes is evident in certain cancer types, such as non-small cell lung cancer (NSCLC) and BC.[6] For example, higher baseline EGFR mutation levels derived from the analysis of ctDNA from NSCLC patients has been associated with increased tumor growth rates.[8,9] In general, an increase in ctDNA levels can serve as an indicator of tumor burden, though the short half-life of ctDNA in circulation prevents the establishment of a specific cut-off concentration value for diagnosing cancer.[9] Simultaneously, surpassing a defined threshold of CTC numbers becomes a clear indicator of the patient's disease status, which may offer valuable insights into prognosis and survival.

An integrated approach, involving measurement of ctDNA and CTC levels combined with mutation profiling, could contribute to a more comprehensive understanding of tumor heterogeneity, facilitating more informed and personalized cancer treatment decisions.[10]

ADVANCES IN THE DETECTION OF CTCS AND CTDNA

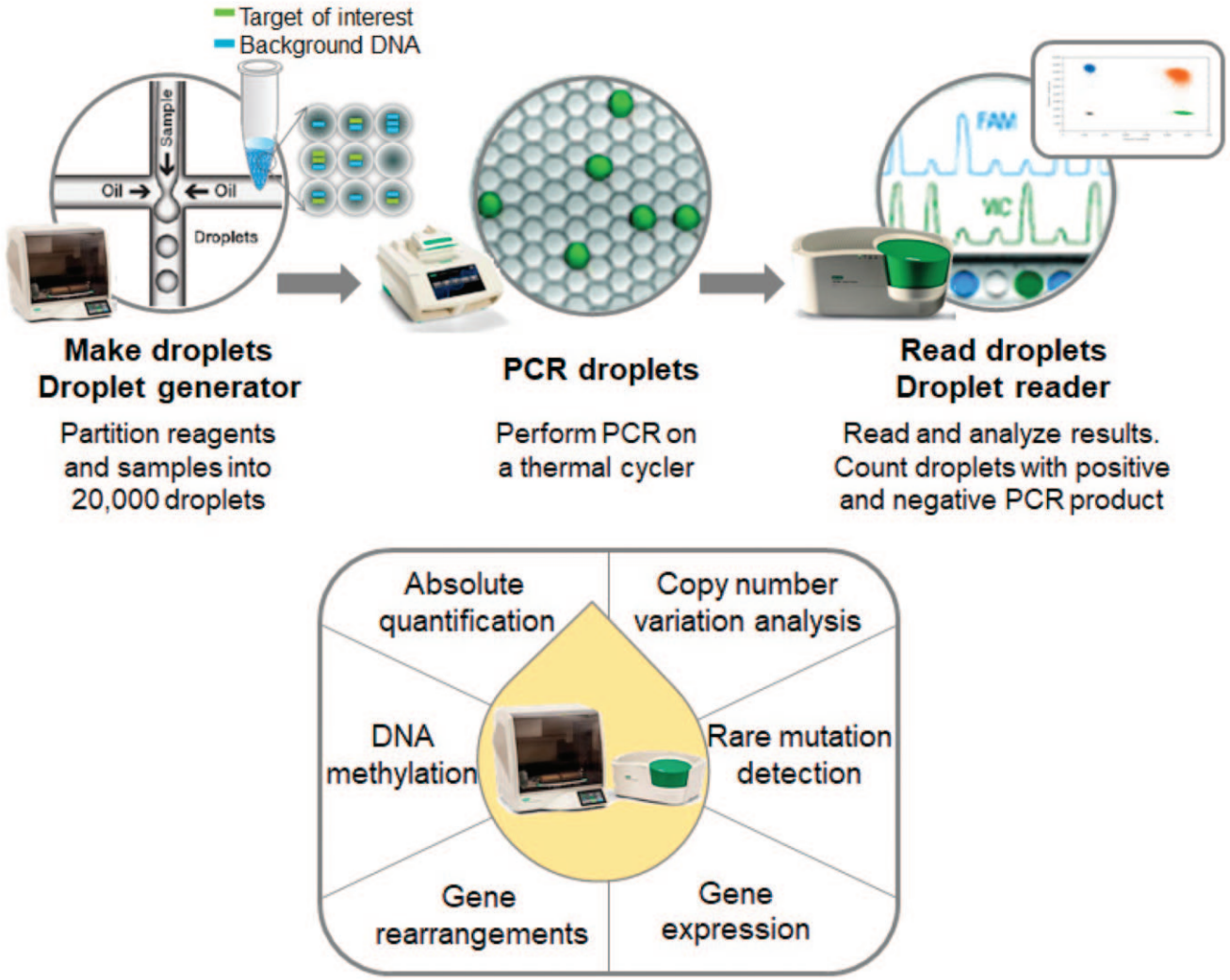
Integration of CTCs into clinical practice as a liquid biopsy analyte will require unbiased, efficient, rapid, and cost-effective capture technologies capable of isolating consistently a sufficient quantity of these rare cells. These capture technologies must also integrate seamlessly with advanced sequencing or quantitative tools and functional assays to produce data essential for accurate therapeutic decision-making. However, the complexity lies in the rarity and phenotypic diversity of CTCs, posing significant challenges for cell enumeration and characterization. As such, efficient CTC enrichment is crucial for reproducible downstream analysis and applications.

In recent years, technological advances have paved the way for the development of highly efficient and automatable techniques used to capture and enrich rare CTCs from liquid biopsy samples. Commercial instruments have emerged as a result of these advances, broadly utilizing antigen-dependent and

antigen-independent approaches. Typically, antibody-based CTC capture processes involve selective CTC capture utilizing biomarkers that are highly expressed on CTCs and minimally expressed on other circulating cells, such as the Epithelial Cell Adhesion (EpCAM) biomarker. Often, this approach is combined with the negative selection of normal blood leukocytes cells using CD45-based methods to enhance assay specificity.[6] However, CTCs transitioning to the mesenchymal state may exhibit low expression of these markers, potentially resulting in them being undetected. Assays capable of detecting multiple biomarkers indicative of cancer progression and metastasis are essential. As such, single-cell multi-omics analysis, coupled with long-term follow-up data, can unveil biomarkers associated with disease progression.[11]

On the other hand, antigen-agnostic detection technologies exploit physical properties such as size, charge, density, or elasticity for the enrichment of CTCs, overcoming challenges associated with biomarker expression. Various methods, including filter-based devices, density gradient centrifugation, capture surfaces, and microfluidic systems employ physical characteristics for CTC detection.[1] Some instruments employ size-based selection of CTCs, which capture cells that are in the CTC size range of 8-30 microns and eliminates most white and red blood cells which are less than 8 microns in size. The size-based capture approach holds a notable advantage in not relying on biomarker expression, that is, even CTCs with varying or alternative biomarker expression profiles can be sorted and collected by size. Some innovative instruments offer a dual functionality of CTC capture and immunostain-based enumeration within a single workflow, all conducted on a microfluidic slide.[12] Microfluidic platforms can also integrate biomarker-based positive and negative selection (eg, EpCAM,

FIGURE 2



Overview of the mutation screening process using droplet-based digital PCR. Adopted from Huerta et al. 2021, under a CC BY 4.0.

EGFR, HER2, and CD45), imaging, and micromanipulation to isolate pure subsets of CTCs. Advances in capture technologies are enabling detailed molecular and functional analyses of CTCs, at both bulk and single-cell levels, moving beyond simple enumeration. Combined with drug phenotyping, single-cell analysis of individual CTCs and CTC clusters can be utilized for the identification of potential therapeutic targets.[1] While CTC capture and downstream analysis may show clinical relevance, many techniques are not yet routinely applied due to existing limitations. Addressing challenges related to CTC epitope expression, cell capture efficiencies, processing of large blood volume, and workflow automation, is essential.

For ctDNA detection technology to be effective, it is crucial to consider that ctDNA accounts only for a small percentage of total cell-free DNA in blood.[4] Despite this fact, advancements in ctDNA analysis have improved detection limits, particularly with third-generation sequencing techniques. High-throughput next-generation sequencing (NGS) and digital PCR (dPCR) have emerged as promising technologies for the detection of mutations in peripheral blood samples.[13] NGS offers extensive information by simultaneously evaluating multiple genetic and epigenetic aberrations over millions of ctDNA molecules, but it is time-consuming, costly, and lacks long-term monitoring capabilities. In contrast, droplet-based dPCR, an innovative dPCR method based on nanoliter-sized water-in-oil emulsion droplet technology, is particularly suitable for the absolute quantification of nucleic acids, including biomarkers of rare CTC subclones and ctDNA. Droplet-based dPCR excels at absolute quantification, rare mutation detection, copy number variation analysis, DNA methylation analysis, and examination of gene rearrangement across various clinical samples (Figure 2).[13] Compared to NGS, droplet-based dPCR is faster, easier to set up, more sensitive, and doesn't require complex bioinformatics analysis.

Application of droplet-based dPCR has successfully demonstrated clinical follow-up potential for various cancers through DNA mutation detection using liquid biopsy samples. The droplet-based multiplex dPCR method has been used to detect KRAS mutations in ctDNA of metastatic colorectal cancer patients, showcasing its potential in monitoring therapy response.[14] Additionally, this method has also been used to monitor therapy response in stage IV melanoma patients.[14] The advancements in PCR-based ctDNA analysis, particularly in droplet-based dPCR methods, have significantly improved the limit of detection and enabled the detection of rare variations.

In summary, integrating data from both CTCs and ctDNA could potentially provide for a more robust evaluation of a tumor's aggressiveness, potential for metastasis, and overall prognosis. Ongoing research focuses on overcoming current limitations in the field, aiming to improve the specificity, reproducibility, and validation of ctDNA and CTC-based detection systems.[2,9,14] Meanwhile, advancements in microfluidics, artificial intelligence, and machine learning for data analysis, and improvements in sequencing technologies aim to enhance the accuracy and reliability of co-analysis. Collaborative efforts between researchers, clinicians, and industry partners are essential for bringing these innovations into routine clinical practice.

LOOKING INTO THE FUTURE

The co-analysis of CTCs and ctDNA represents a paradigm shift in our approach to understanding cancer tumor heterogeneity. Long-term monitoring of phenotypic, genomic, and epigenetic changes in CTCs and ctDNA mutations would provide valuable insights into the effectiveness of therapeutic interventions.[1] By correlating genetic alterations detected in ctDNA with captured CTCs characteristics, researchers can establish connections between genomic, phenotypic, and functional changes and gain a better understanding of tumor biology. The potential clinical applications of this approach, from personalized medicine to dynamic treatment monitoring, hold immense promise for improving cancer outcomes by guiding adjustments to treatment strategies. While challenges persist, ongoing research and technological innovations pave the way for a future where the co-analysis of CTCs and ctDNA becomes a routine and invaluable tool in the fight against cancer. ◆

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BIOGRAPHIES

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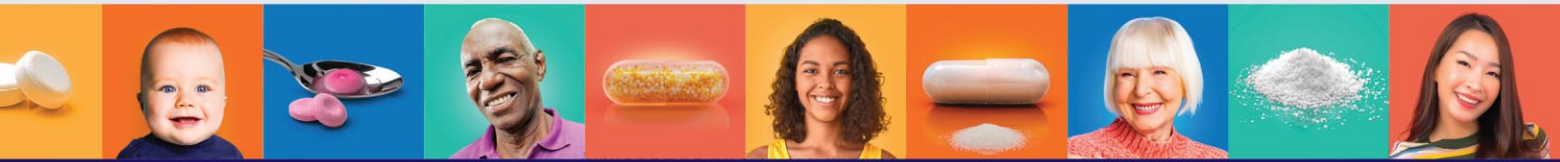

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