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Taming Bioavailability & Solubility

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Taming Bioavailability & Solubility

"More than 75 bioavailability enhancement technologies are presently available in the market. Most (55%) support solubility enhancement, and nearly 70% provide bioavailability enhancement services for solids, followed by liquids and fine particles/powders. Shifting focus of drug developers towards development of lipophilic drug compounds is anticipated to drive the demand for bioavailability enhancement technologies and services in the next 13 years. Consequently, the outsourced commercial demand for bioavailability enhancement is projected to increase."

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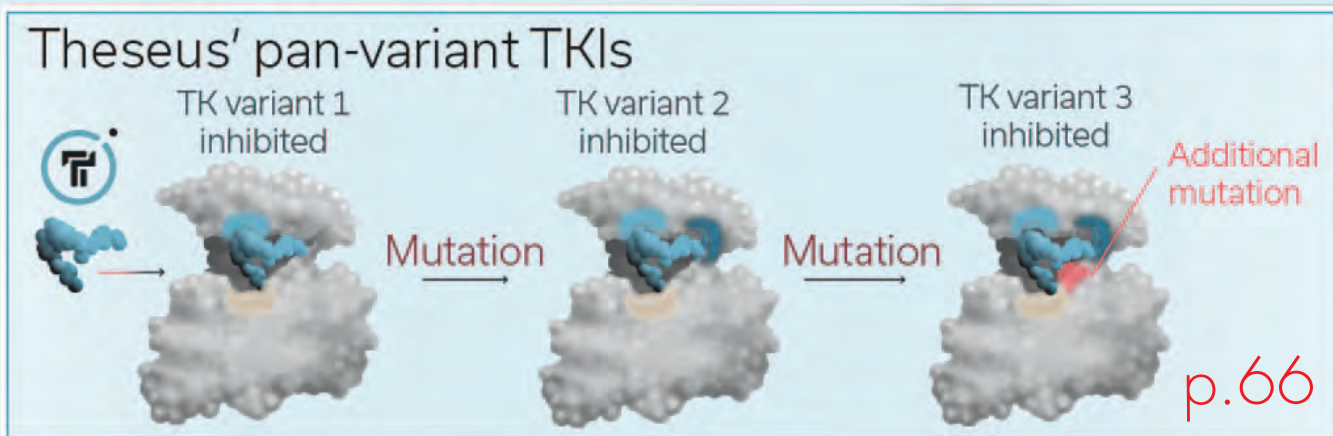
Tim Clarkson, PhD, says the goal in targeted oncology is to achieve pan-variant inhibition and, ideally, pan-variant inhibition should be accomplished with a single agent, avoiding the potential complications and toxicities of drug combinations.

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Pan-Variant Inhibitors

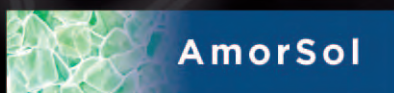
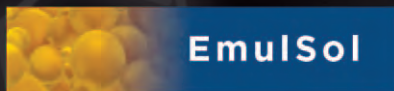
"Pan-variant inhibitors simultaneously cut off all the tumor's routes to treatment escape via that target protein, so they can both suppress the emergence of resistance mutations during early lines of therapy, and address those mutations after they have already emerged during later lines of therapy. Thus, they have the potential to provide substantial benefit to patients in both earlier and later lines of therapy relative to current standards of care."



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Cue Biopharma Enters Strategic Collaboration & Option Agreement With Ono Pharmaceutical

Cue Biopharma, Inc. recently announced a collaboration and option agreement with Ono Pharmaceutical Co., Ltd. for CUE-401, a bispecific protein designed to induce and expand regulatory T cells (Tregs) for the treatment of autoimmune and inflammatory diseases.

The strategic collaboration with Ono is an important advancement in Cue Biopharma's corporate development plan to seek third party support to further develop its CUE-400 series and provides dedicated resources and capabilities to help advance CUE-401 toward the clinic. In preclinical studies, CUE-401 has demonstrated induction and expansion of Tregs, with the potential to address a broad range of autoimmune and inflammatory diseases.

Under the terms of the agreement, Ono will pay Cue Biopharma an upfront payment and fully fund all research activities related to CUE-401 through a specified option period. During this option period Cue Biopharma will be responsible for the research and development of CUE-401. Upon Ono's exercise of its option to license CUE-401, Cue Biopharma will receive an option exercise payment and be eligible for development and commercial milestone payments up to an aggregate of approximately \$220 million, as well as tiered royalties on sales. Upon any such exercise, Ono will receive worldwide rights to develop and commercialize CUE-401, with Cue Biopharma retaining a 50% co-development and co-commercialization right in the US.

"This strategic collaboration with Ono Pharmaceutical, a leading Japanese pharmaceutical company with a track record

of scientific innovation, is a significant accomplishment for Cue Biopharma, as it allows us to further develop this promising biologic through the support of a strategic partner," said Daniel Passeri, Chief Executive Officer of Cue Biopharma. "Through this important partnership we have secured resources and capabilities necessary to help advance CUE-401 towards the clinic, while preserving potential value to our shareholders through a 50:50 collaboration right for the US market."

CUE-401 is a preclinical, bispecific fusion protein designed to induce and expand regulatory T cells (Tregs) through the delivery of transforming growth factor beta (TGF- β) and interleukin 2 (IL-2) with therapeutic potential across a range of T-cell mediated autoimmune and inflammatory diseases.

Ono Pharmaceutical Co., Ltd., headquartered in Osaka, is an R&D-oriented pharmaceutical company committed to creating innovative medicines in specific areas. Ono focuses its research on oncology, immunology, neurology and specialty research with high medical needs as priority areas for discovery and development of innovative medicines.

Cue Biopharma, a clinical-stage biopharmaceutical company, is developing a novel class of injectable biologics to selectively engage and modulate disease-specific T cells directly within the patient's body. The company's proprietary platform, Immuno-STAT (Selective Targeting and Alteration of T cells) and biologics are designed to harness the body's intrinsic immune system as T cell engagers without the need for ex vivo manipulation or broad systemic immune modulation.

PDS Biotech Completes Successful Meeting With FDA for Triple Combination of PDS0101, PDS0301 & a Commercial Immune Checkpoint Inhibitor

PDS Biotechnology Corporation recently announced the successful completion of a Type B meeting with the US FDA for a combination therapy of PDS0101, PDS0301, and an FDA-approved immune checkpoint inhibitor (ICI) for the treatment of recurrent/metastatic human papilloma virus (HPV)-positive, ICI refractory head and neck cancer. Head and neck cancers are the most common of all HPV-positive cancers and the number of cases is growing rapidly, according to the National Cancer Institute (NCI), one of the National Institutes of Health (NIH). There remains a critical unmet medical need to develop new treatment options for patients who have failed treatment with ICIs.

In recent interactions with the FDA, PDS Biotech has confirmed the required contents of the study design for a potential registrational trial of the combination of PDS0101, PDS0301 and a commercial immune checkpoint inhibitor. PDS0101, PDS Biotech's lead candidate, is a Versamune-based investigational immunotherapy designed to stimulate a potent targeted T cell attack against HPV16-positive cancers. PDS0301 is a novel, proprietary investigational tumor-targeting fusion protein of Interleukin 12 (IL-12) that enhances the proliferation, potency and longevity of T cells in the tumor microenvironment, and is designed to overcome tumor immune suppression utilizing a different mechanism from checkpoint inhibitors. The combination of Versamune and IL-12 is patented by PDS Biotech. In a National Cancer Institute (NCI)-led clinical trial in advanced HPV-positive

ICI refractory patients, the combination of PDS0101 and PDS0301 administered with an investigational bi-functional ICI resulted in a median overall survival of 21 months, which compares favorably to the historical median survival of 3-4 months.

PDS0101, PDS Biotech's lead candidate, is a novel investigational human papilloma virus (HPV)-targeted immunotherapy that stimulates a potent targeted T cell attack against HPV-positive cancers. PDS0101 is given by a simple subcutaneous injection in combination with other immunotherapies and cancer treatments. Interim data suggests PDS0101 generates clinically effective immune responses, and the combination of PDS0101 with other treatments can demonstrate significant disease control by shrinking tumors, delaying disease progression and/or prolonging survival. The combination of PDS0101 with other treatments does not appear to compound the toxicity of other agents.

PDS0301 is a novel investigational fusion protein of a tumor-targeting antibody and Interleukin 12 (IL-12) that enhances the proliferation, potency and longevity of T cells in the tumor microenvironment. Together with Versamune-based immunotherapies PDS0301 works synergistically to promote a targeted T cell attack against cancers. PDS0301 is given by a simple subcutaneous injection. Clinical data suggest the addition of PDS0301 to Versamune-based immunotherapies can demonstrate significant disease control by shrinking tumors and/or prolonging survival in recurrent/metastatic cancers with poor survival prognosis.

EyePoint & Rallybio Announce Research Collaboration

Rallybio Corporation and EyePoint Pharmaceuticals, Inc recently announced a research collaboration. The partnership will evaluate sustained delivery of Rallybio's inhibitor of complement component 5 (C5) using EyePoint's proprietary Durasert technology for sustained intraocular drug delivery. The initial focus will be on geographic atrophy, an advanced form of age-related macular degeneration that leads to irreversible vision loss.

"We are excited to begin this research collaboration to explore the combination of Rallybio's C5 inhibitor with our bioerodible Durasert sustained-release drug delivery technology to develop a potential long-acting treatment for geographic atrophy," said Jay Duker, MD, President and Chief Operating Officer of EyePoint Pharmaceuticals. "Geographic atrophy associated with dry macular degeneration is a devastating eye disease, and the inhibition of complement is a proven treatment pathway. We hope to leverage our Durasert technology in this collaboration to create a potential best-in-class, long-acting intravitreal insert, which we believe could provide a more desirable option for patients given that the existing approved therapy is injected every 1 to 2 months."

"EyePoint's proprietary Durasert sustained release technology combined with our differentiated C5 inhibitor offers the potential for a new, long-acting therapeutic for the treatment of eye diseases. Importantly, it's a potential treatment option that requires less frequent intraocular injections with comparable efficacy that could provide a greatly improved alternative for patients. The use of C5 inhibitors for the treatment of eye disease has shown great promise, and we are excited to initiate this research in the hopes of improving the lives of patients suffering from eye diseases, such as geographic atrophy," said Steve Uden, MD, President and Chief Operating Officer of Rallybio.

Under the terms of the research collaboration, EyePoint and Rallybio will collaborate to explore and assess the viability of utilizing Rallybio's C5 inhibitor in EyePoint's sustained release Durasert technology, with the intention to expand the collaboration upon mutual agreement following the evaluation.

Approximately 1 million people in the US are affected by geographic atrophy (GA), a progressive, advanced stage of dry age-related macular degeneration (AMD) that can occur in patients with the wet form of AMD as well. GA is characterized by atrophic lesions in the central region of the macula, which cause irreversible vision loss and can lead to legal blindness. Patients may experience scotomas or "blind spots" in their central vision, along with distorted vision and decreased contrast sensitivity. One or both eyes can be affected. As currently available US FDA-approved treatments for GA are limited in both choice and duration of action, there remains a significant unmet need for safe, effective and durable treatment options for patients living with this chronic disease.

EyePoint Pharmaceuticals (Nasdaq: EYPT) is a company committed to developing and commercializing therapeutics to help improve the lives of patients with serious eye disorders. Rallybio is a clinical-stage biotechnology company committed to identifying and accelerating the development of life-transforming therapies for patients with severe and rare diseases.

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Ajinomoto Bio-Pharma Services Successfully Develops Highly Functional Ancestral RNA Ligase

Ajinomoto Bio-Pharma Services, a leading provider of biopharmaceutical contract development and manufacturing services, recently announced the development of a new enzyme for double strand oligonucleotide formation with high productivity.

In collaboration with researchers from the University of Shizuoka, Aji Bio-Pharma succeeded in developing a highly functional artificial RNA ligase using the ancestral design method. It was found that this artificial RNA ligase has higher thermostability than natural RNA ligase as well as superior ligation activity for RNA fragments containing xenonucleic acid.

When using the natural RNA ligase for RNA fragments (including xenonucleic acid) as reaction substrates to synthesize a marketed siRNA drug substance, the yield was only 20% after 24 hours of reaction. In contrast, when using the highly functional artificial RNA ligase, the reaction yield improved to 80% under the same conditions, confirming that it has properties suitable for enzymatic synthesis of nucleic acid medicines. This approach attains more productive and environmentally safe oligonucleotide synthesis when compared to the conventional method.

"We are excited to provide new research to our partners and support them in their efforts to supply lifesaving therapeutics," said Yusuke Hagiwara, Senior Researcher, Ajinomoto Bioscience & Fine Chemicals Research Laboratories. "This discovery for siRNA is a great example of Aji Bio-Pharma continuing to provide reliable and innovative solutions to our clients."

The RNA fragments used as reaction substrates can be pro-

duced by not only conventional solid phase synthesis, but also by Ajinomoto Co.'s AJIPHASE technology, especially in large quantities and with high purity. This achievement is expected to be applied as one of the technologies that enables the mass production of nucleic acid drugs with high efficiency and high purity. This result was presented in the journal *Applied and Environmental Microbiology* published by the American Society for Microbiology.

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

As its pharmaceutical arm, Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization (CDMO) with sites in Belgium, United States, Japan, and India, providing comprehensive development, cGMP manufacturing, and aseptic fill finish services for small through large molecule APIs and intermediates.

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

First Subject Dosed in Small Pharma's First-in-Human Phase 1 Clinical Trial

Small Pharma Inc. recently confirmed the first subject has been dosed in a Phase 1 study evaluating SPL028, its deuterated N, N-dimethyltryptamine (DMT) candidate, with supportive therapy in healthy volunteers. This is the first-in-human trial investigating the profile of SPL028, the company's proprietary molecule with Composition of Matter protection.

Small Pharma's preclinical studies suggest that SPL028 offers a similar safety and pharmacological profile to its lead candidate SPL026, or DMT, while being differentiated by its pharmacokinetics. The company aims to deliver a treatment with an extended psychedelic experience in comparison to 20-25 minutes with SPL026, but still significantly shorter than the experience of other psychedelics, such as psilocybin and lysergic acid diethylamide (LSD). Through the SPL028 clinical program, Small Pharma is exploring whether an extended duration could offer a treatment tailored for other mental health conditions in addition to depression. Additionally, the pharmacokinetic profile of SPL028 offers the opportunity to explore additional routes of administration, potentially expanding patient convenience.

The Phase 1 study is a randomized, blinded, placebo-controlled, dose-escalating study being conducted at MAC Clinical Research in Manchester, England. It is designed to evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of both intravenous (IV) and intramuscular (IM) administration of SPL028.

Dr. Carol Routledge, Chief Medical and Scientific Officer, said "With the SPL028 trial now underway, we look forward to

learning more about its pharmacokinetic and pharmacodynamic properties in humans. Comparison of the IM and IV routes of administration in this study aims to create options for patients and physicians, which may help to expand convenience and accessibility. We expect that the results from this Phase 1 study will enable us to make a data-driven decision in selecting the dose and route of administration to take forward into a patient study."

George Tziras, Chief Executive Officer, added "This is a significant milestone for Small Pharma, with our second key program now in clinical development. The recent announcement on January 25, 2023 of our positive Phase 2a results demonstrates proof-of-concept for SPL026 in treating major depression. These encouraging results also provide support for our portfolio of DMT-based assets, and give us confidence in driving forward both our SPL026 and SPL028 programs."

Small Pharma is a biotechnology company progressing a pipeline of short-duration psychedelic-assisted therapies for the treatment of mental health conditions. The company's current focus is on exploring new therapeutic approaches for depression. Small Pharma's lead candidate, SPL026, is a proprietary synthetic formulation of DMT. The company is advancing clinical programs of SPL026 and SPL028 with supportive therapy for the treatment of mental health conditions, and was granted an Innovation Passport designation from the UK Medicines and Healthcare products Regulatory Agency (MHRA) for IV SPL026 with supportive therapy for Major Depressive Disorder. In addition, Small Pharma has a pipeline of proprietary preclinical assets in development.

Acumen Pharmaceuticals Completes Enrollment in Phase 1 Trial of First Monoclonal Antibody Developed to Selectively Target Toxic A β Oligomers in Patients With Early Alzheimer's Disease

Acumen Pharmaceuticals, Inc. recently announced the completion of enrollment in its Phase 1 INTERCEPT-AD trial of ACU193 in patients with early Alzheimer's disease. Acumen is on track to report topline results, including safety and proof-of-mechanism data, in the third quarter of 2023, which is earlier than previously expected.

"Today's announcement marks an important milestone for Acumen and the Alzheimer's community as we continue to explore ACU193 as a potential therapeutic option for people with early Alzheimer's disease," said Daniel O'Connell, President and Chief Executive Officer of Acumen Pharmaceuticals. "ACU193 builds on decades of scientific evidence that points to the role of soluble amyloid beta oligomers as primary and persistent toxins in Alzheimer's pathology. By targeting toxic oligomers, we hope to expand the understanding of targets beyond deposited amyloid plaques which we believe could provide patients with safer and more effective treatment options."

The Phase 1 INTERCEPT-AD trial enrolled 65 subjects across 17 active sites in the United States. This randomized, placebo-controlled Phase 1 trial is designed to assess safety and proof of mechanism of ACU193. The trial was initiated based on encouraging nonclinical studies of ACU193 that support the selective targeting of A β Os.

ACU193 is the first clinical-stage monoclonal antibody developed to selectively target soluble A β Os, which are among the most toxic and pathogenic forms of A β relative to A β monomers and deposited amyloid plaque. Toxic soluble A β Os have been found to interact within synapses, which leads to altered neuronal

function, and can initiate and perpetuate the process of neurodegeneration.

ACU193 is a humanized monoclonal antibody (mAb) discovered and developed based on its selectivity for soluble amyloid beta oligomers (A β Os), which Acumen believes are the most toxic and pathogenic form of A β , relative to A β monomers and amyloid plaques. Soluble A β Os have been observed to be potent neurotoxins that bind to neurons, inhibit synaptic function and induce neurodegeneration. By selectively targeting toxic soluble A β Os, ACU193 aims to directly address what a growing body of evidence indicates is a primary underlying cause of the neurodegenerative process in Alzheimer's disease. ACU193 has been granted Fast Track designation for the treatment of early Alzheimer's disease by the U.S. Food and Drug Administration.

INTERCEPT-AD is a Phase 1, US-based, multi-center, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and tolerability, and establishing clinical proof of mechanism, of ACU193 in patients with early Alzheimer's disease (AD). Sixty-five individuals with early AD (mild cognitive impairment or mild dementia due to AD) have been randomized into this first-in-human study of ACU193. The INTERCEPT-AD study consists of single-ascending-dose (SAD) and multiple-ascending-dose (MAD) cohorts and is designed to evaluate the safety, tolerability, pharmacokinetics (PK), and target engagement of intravenous doses of ACU193. The study has completed enrollment across multiple investigative sites located in the United States.

QSAM Biosciences Completes Enrollment of Initial Cohort in its Phase 1 Study of CycloSam Targeting Metastatic Bone Cancer

QSAM Biosciences Inc. recently announced the completion of enrollment in the first participant grouping (cohort) of its Phase 1 study evaluating CycloSam in the treatment of bone cancer. The last participant dosed was a breast cancer patient with active metastatic bone cancer.

QSAM's study is a multiple center, open label, dose escalation clinical trial intended to determine the maximum tolerated dose of CycloSam in patients, and also assess early safety and efficacy signals. The completed cohort of three participants received the lowest dosage of CycloSam in the study. The total dosage of the active radioisotope Samarium-153 to be received by the second cohort, expected to commence in early Q2 2023, will be 50% higher.

"Completion of our first cohort of patients is an important milestone for QSAM," said Douglas R. Baum, CEO. "We are pleased with the early results, and are looking forward to continuing enrollment in subsequent cohorts in this important clinical trial evaluating the early safety and efficacy of CycloSam in patients with metastatic bone cancer."

The most recent participant in QSAM's clinical trial was a patient with breast cancer that had metastasized to the bone, a serious and life-threatening disease for which there is an unmet need by patients and an area of high interest by management for the clinical trials and product development of CycloSam. The only two commercially available radiotherapies for bone cancer,

to management's knowledge, are only FDA approved for use in men who have bone metastases from prostate cancer. CycloSam, which delivers its radioactive payload using a chelant that is highly targeted to high calcium turnover in bone and bone tumors, is currently being studied in a clinical trial for both male and female patients with bone cancer that has metastasized from the breast, lungs, prostate, or other organs, as well as patients with cancer that has originated in the bone, such as osteosarcoma and Ewing's Sarcoma – diseases that mostly affect children and young adults.

Adults with bone cancer that has migrated or metastasized from the breast, lung, or prostate is common and frequently fatal. QSAM is dedicated to developing its CycloSam product for this important patient population, and patients with any of these bone cancer types are eligible for this clinical trial. Osteosarcoma, while still a rare pediatric disease, is the most common form of bone cancer in children and young adults (ages 15-39) with primary high-grade bone malignancy, and Ewing's Sarcoma bone cancer is the second most common form of bone cancer in children. According to the Cancer Facts & Figures 2021 produced by the American Cancer Society there are about 400,000 new cases of malignant bone metastasis (which includes approximately 14% of the 265,000 women diagnosed with breast cancer each year), and 3,610 new cases of primary bone cancer diagnosed in the US each year.

Absci Expands in Europe With Launch of New Innovation Center & Additional Senior Leadership in Switzerland

Absci Corporation recently announced its expansion into the European pharmaceutical market with the opening of its Innovation Center, located in Zug, Switzerland. The Zug Innovation Center brings Absci's AI drug creation platform to the global stage and taps into the European pharma and biotech ecosystem. Absci welcomed two senior executives to lead its drug creation team: Christine Lemke, DVM, MBA, SVP of Portfolio & Growth Strategy, and Christian Stegmann, PhD, SVP of Drug Creation.

"Absci's European presence signals a new phase in expanding our strategic R&D portfolio and building Absci's own drug development pipeline," said Andreas Busch, Absci's Chief Innovation Officer. "The Zug Innovation Center taps into important potential partners, global talent, and AI capabilities in Europe and beyond. Drs. Lemke and Stegmann are esteemed leaders who bring tremendous experience and an impressive track record to help lead our strategic portfolio and global expansion."

"The Zug Innovation Center brings Absci's drug creation platform to the heart of European innovation," said Sean McClain, founder and CEO of Absci. "Zug is a leading biotech hub for bringing drugs to market. Absci is tapping into its talent and technology ecosystem to realize our mission of bringing life-changing biologics to patients faster, through the power of generative AI and our expansion into the region."

Dr. Lemke previously served as Head of Global Corporate Development at Ferring International Center SA. A seasoned international executive, she brings substantial corporate development and operations expertise to Absci. For global

biopharmaceutical companies, including Bayer, Shire, and Takeda, Dr. Lemke delivered multiple global, transformative strategic projects. Her experience in nearly every aspect of drug discovery and development will shape Absci's R&D strategy with an emphasis on bringing life-changing medicines to patients.

"Based on my experience in the industry, Absci presents a once-in-a-lifetime opportunity to transform the drug creation process," said Dr. Lemke. "It's a rare opportunity to work with a team of this caliber, and I'm optimistic we can create better biologics for patients faster."

Dr. Stegmann is an accomplished R&D leader with a track record of building teams that successfully bring novel molecules into clinical development. Dr. Stegmann previously served as the VP of Research and Non-clinical Development at CSL Vifor, where he built a highly innovative R&D portfolio in nephrology and iron deficiency. Prior to that, he held various R&D leadership roles at Bayer, most recently as Senior Director of its Precision Cardiology Laboratory, leading a flagship collaboration with the Broad Institute of MIT and Harvard.

"Generative AI has the potential to power the next era of drug creation, and Absci is leading the way in what's possible," said Dr. Stegmann. "Creating meaningful innovative therapies for patients is a challenging and demanding endeavor with many components that have to mesh perfectly. Using Absci's unique capabilities in AI, I look forward to making this endeavor more efficient and successful to improve patients' lives."

Rhythm Pharmaceuticals Announces Acquisition of Xinvento B.V. & Portfolio of Investigational Therapeutics

Rhythm Pharmaceuticals, Inc. recently announced Rhythm's Netherlands subsidiary, Rhythm Pharmaceuticals Netherlands B.V., acquired Xinvento B.V., a Netherlands-based biotech company focused on developing therapies for congenital hyperinsulinism (CHI). CHI is a rare genetic disease in which cells secrete excess insulin, causing hypoglycemia, which can result in serious health outcomes including seizures, coma, permanent brain damage, and death.

Xinvento was founded in 2021 by Claudine van der Sande, an experienced biopharmaceutical leader who previously held positions at Roche and Sanofi, and whose first-hand experience as a caregiver to her son living with CHI inspired her mission to seek a more effective treatment for CHI patients. Ms. van der Sande partnered with Dr. Piet Wigerinck, a medicinal chemist who served as chief scientific officer of Galapagos for 10 years, to lead the scientific effort. Xinvento is developing novel investigational therapeutic candidates designed to improve the care of patients with CHI.

"As a mother and primary caregiver to a child with CHI, Claudine knows that there is significant unmet need for new treatment options that can safely lower the frequency of hypoglycemic events and help minimize the incidence of irreversible brain damage in people born with CHI. In 2 short years, we believe she has driven a nimble, science-focused organization towards bringing a highly promising therapeutic candidate into the clinic," said

David Meeker, MD, Chair, President and Chief Executive Officer of Rhythm. "We are excited for the opportunity to expand our pipeline into CHI, a rare disease that is well aligned with our corporate strategy and our focus on rare endocrinology indications. We look forward to entering the clinic with a new therapeutic candidate in 2024."

"I am confronted daily with the constant challenges and fears of living with CHI and the urgent need for an effective new treatment. I believe Rhythm's deep clinical development, regulatory and commercial experience in rare diseases makes it the ideal partner to accelerate Xinvento's CHI program," said Ms. van der Sande. "I'm thrilled to join the Rhythm team to continue our work to bring a new therapy to patients and families who need improved options to treat this difficult, chronic disease."

According to the terms of the acquisition agreement, Rhythm B.V. will purchase 100 percent of Xinvento's fully diluted equity for an upfront payment of \$5 million (subject to customary adjustments) with an additional payment of up to \$6 million in pre-clinical development milestones and up to an additional \$50 million payable upon certain U.S. or EU regulatory approvals. Rhythm B.V. will also pay up to an additional \$150 million in certain commercial net sales milestones related to the lead candidate or a second molecule, in the event a second molecule is selected, developed and approved.

Eterna Therapeutics Enters Option & License Agreement With Lineage Cell Therapeutics to Develop Hypoimmune Pluripotent Cell Lines for Multiple Neurology Indications

Eterna Therapeutics Inc. recently announced it has entered into an exclusive option and license agreement with Lineage Cell Therapeutics, Inc. for the development of novel induced hypoimmune pluripotent stem cell (iPSC) lines, which Lineage will evaluate for development into cell transplant therapies. The new cell lines to be developed by Eterna will support the potential creation of additional product candidates at Lineage, specifically for the treatment of certain central nervous system (CNS) disorders and other neurology indications. Eterna is the exclusive licensee of the key intellectual property underlying this collaboration.

"The cell therapy expertise demonstrated by Lineage makes them an attractive partner to deploy our mRNA cell engineering platform for the generation of novel gene-edited iPSC lines for neurological applications," said Matt Angel, PhD, CEO of Eterna. "At Eterna, we have expertise in creating gene-edited iPSC lines using our extensively patented mRNA cell engineering technologies. We look forward to collaborating with the Lineage team on this project and working with them to develop these powerful tools for the generation of new, intelligently engineered cell therapy product candidates in the CNS space."

Under the Agreement, Eterna plans to conduct certain gene-editing activities and provide materials to Lineage for evaluation. The Agreement provides Lineage an option to obtain an exclusive license to utilize and sublicense the novel gene-edited cell lines

for preclinical, clinical, and commercial purposes in the field of CNS diseases. A feature of the starting cell line is the targeted deletion of the beta 2 microglobulin (B2M)-gene, which is designed to reduce the immunogenicity of product candidates derived from the lines by inhibiting rejection by CD8+ T cells. Lineage expects this attribute will expand the edited cell lines' overall utility, including for non-immune privileged or non-human leukocyte antigen (HLA) matched indications. Additional planned gene edits may further differentiate the cell line from others currently in use by competitors. Financial terms were not disclosed.

"This agreement provides the opportunity to combine insights obtained from our dry age-related macular degeneration program with new tools, to broaden the scope of our technology and may help deliver solutions for a wider range of diseases. The engineering of desirable properties into cell lines can also lead to treatments that are highly differentiated from our competitors," added Brian M. Culley, Lineage's CEO. "The initial cell lines we envision bringing into the clinic through this agreement will utilize proprietary mRNA-based gene-editing technology developed by Eterna's CEO, Dr. Matt Angel. It is natural that we would look to introduce aspects of gene editing, hypoimmunity, and additional pluripotent cell lines alongside our existing directed differentiation capabilities in the furtherance of our overall goal of becoming a comprehensive leader in cell therapy."

Amydis Announces Enrollment of Cerebral Amyloid Angiopathy Participants in Phase 1/2a Retinal Tracer Trial

Amydis Inc. recently announced initiation of enrollment of patients with cerebral amyloid angiopathy (CAA), an age-associated disease in which a protein called amyloid beta (A β) builds up on the walls of the arteries in the brain increasing the risk for stroke and dementia. CAA develops in up to 23% of the general population with aging, and it occurs at a higher rate of ~48% in people with Alzheimer's disease due to overlapping etiology. The Randomized Open, Blinded Endpoint Phase 1/2a trial funded in part by a \$3-million commercialization readiness pilot grant from the National Institute of Aging at National Institutes of Health (NIH) is evaluating the safety, tolerability, pharmacokinetics, and activity of AMDX-2011P, a proprietary small molecule ocular imaging agent targeting deposits of A β in the retina of patients with CAA. This trial (NCT05709314) is part of a larger "basket trial" that also includes a study (NCT05542576) evaluating Amydis ocular tracer technology in amyotrophic lateral sclerosis and Parkinson's disease. These studies are being conducted at two sites in Southern California. Additional information regarding the clinical trial, may be found at <https://probeclinicaltrial.com/home>.

Even with current expensive imaging tests such as MRI, CT scans, and PET amyloid tests, physicians are not able to confidently diagnose CAA without a sample of brain tissue. The Amydis retinal tracer is designed to be used with conventional ocular

imaging cameras already in clinical practice and provides the potential to be able to quantify the presence of vascular deposits of A β directly in a central nervous system (CNS) tissue, the retina, at micron-level resolution. The Amydis test is positioned as a more affordable and accessible test available to physicians.

"We are thrilled to expand our basket trial to enroll patients with CAA," said Dr. Stella Sarraf, Chief Executive Officer and Founder of Amydis. "Our mission in developing the Amydis ocular tracer for CAA is to enable physicians to take better care of patients by facilitating earlier intervention and avoiding prescription of medications contraindicated in this disease, thereby decreasing the likelihood of their patients having a hemorrhagic stroke."

Amydis is developing novel, patent-protected molecules – "ocular tracers" – that enable direct visualization of CNS disease-related molecular changes (biomarkers) in the eye. With this first-in-class capability, Amydis is poised to revolutionize the ability of physicians and researchers to explore the eye for a broad spectrum of diseases that have to date required long-term clinical evaluation and the use of invasive testing for definitive diagnosis. The company has a discovery platform and proprietary know-how that position it as first mover and a global leader in developing ocular tracers for human diseases. The future of effective, sustainable healthcare depends on knowledge gained through early diagnostics.

Icosavax Granted FDA Fast Track Designation for RSV & hMPV Vaccine Candidate

Icosavax, Inc. recently announced the US FDA has granted Fast Track designation for IVX-A12, a bivalent respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) VLP vaccine candidate, in older adults 60 years of age and older.

According to the FDA, Fast Track is a process designed to facilitate the development and expedite the review of investigational drugs to treat serious conditions and fulfill an unmet medical need. An investigational drug that receives Fast Track designation may be eligible for more frequent interactions with the FDA to discuss the candidate's development plan and, if relevant criteria are met, eligibility for Accelerated Approval and Priority Review.

"We are delighted to have received the Fast Track designation for IVX-A12, which we believe highlights the unmet medical need that could be addressed by developing a bivalent vaccine combination of RSV and hMPV," said Niranjana Kanethasan, Chief Medical Officer of Icosavax. "IVX-A12 is differentiated as the most advanced vaccine candidate against these two leading causes of pneumonia in older adults. RSV is estimated to cause approximately 177,000 hospitalizations and 14,000 deaths each year in this population in the US alone, and data support similar morbidity and mortality for hMPV. We will utilize the benefits of this important regulatory milestone to work to optimize the IVX-A12 development plan. In addition, we look forward to the upcoming topline results of our Phase 1 study, and thereafter to the planned initiation of our Phase 2 trial."

In October 2022, Icosavax announced the initiation of a Phase 1, randomized, observer-blinded, placebo-controlled, multi-center study of IVX-A12, with and without CSL Seqirus' proprietary adjuvant MF59, in up to 120 healthy older adults aged 60 to 75 years. Icosavax anticipates announcing topline interim results from this Phase 1 trial in mid-2023, with subjects thereafter followed through 12 months after vaccination. The company currently plans to initiate a Phase 2 trial for IVX-A12 in 2H 2023.

Icosavax is a biopharmaceutical company leveraging its innovative VLP platform technology to develop vaccines against infectious diseases, with an initial focus on life-threatening respiratory diseases and a vision for combination and pan-respiratory vaccines. Icosavax's VLP platform technology is designed to enable multivalent, particle-based display of complex viral antigens, which it believes will induce broad, robust, and durable protection against the specific viruses targeted. Icosavax's pipeline includes vaccine candidates targeting respiratory syncytial virus (RSV), human metapneumovirus (hMPV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and an emerging program in influenza. Icosavax was formed in 2017 to advance the breakthrough VLP technology from the Institute for Protein Design at the University of Washington with the goal to discover, develop, and commercialize vaccines against infectious diseases. Icosavax is located in Seattle.

Quotient Sciences Expands Formulation Development Capabilities to Further Accelerate Drug Development Timelines

Quotient Sciences, the drug development and manufacturing accelerator, recently announced it has completed an expansion of its early phase formulation development capabilities for oral dosage forms at its Nottingham, UK, facility. The expanded services build upon the site's existing formulation capabilities and increases capacity to support fully integrated drug development programs through the company's flagship platform, Translational Pharmaceuticals®.

Over the past 30 years, Quotient Sciences has built a strong reputation for developing both simple and complex, fit-for-phase formulations for small molecules and peptides. With this latest investment, the company has expanded its high containment laboratory capacity to support oral drug programs, including immediate-release, modified-release, tablet, and multi-particulate dosage forms for highly potent compounds.

Andy Lewis, Global Vice President of Integrated Pharmaceutical Sciences at Quotient Sciences, said "At Quotient Sciences, our expertise in formulation development is underpinned by our unique track record in clinical research. Having both biopharmaceuticals and clinical knowledge in-house, coupled with our experience from formulating over 1,500 molecules, enables us to accelerate the development process for our customers. With these expanded capabilities, we can start formulation development work even earlier for our customers, allowing for projects to start

faster and turnaround times to be reduced, which in turn will speed up development timelines. Importantly, the new equipment and process trains are fully integrated with our existing capabilities, so at the appropriate point we can quickly transition drug programs downstream into GMP clinical trial manufacturing, saving our customers precious time in advancing innovative medicines into the clinic."

Mark Egerton, CEO of Quotient Sciences, added "Quotient Sciences' mission is to help get new medicines to patients faster and over the course of the last decade we've been investing in capabilities to support that. We place a great importance on supporting customer demand and will continue to actively increase our formulation tool kit to provide more integrated solutions under a single organization to streamline the outsourcing paradigm for our customers."

Quotient Sciences is a drug development and manufacturing accelerator providing integrated programs and tailored services across the entire development pathway. Cutting through silos across a range of drug development capabilities, we save precious time and money in getting drugs to patients. Everything we do for our customers is driven by an unswerving belief that ideas need to become solutions, and molecules need to become cures, fast. Because humanity needs solutions, fast. For more information, visit quotientsciences.com.

SPECIAL FEATURE


Solubility & Bioavailability: Difficult Beasts to Tame

By: Cindy H. Dubin, Contributor

Solubility remains challenging as new molecules coming out of discovery are poorly soluble. Less soluble means the molecules can't be absorbed and therefore, can't be solubilized. Factors responsible for poor solubility stem from high melting (MP) and high partition coefficient (logP) of molecules. Regardless of their structures, the solubility is limited in water because most of them have a tendency to prefer organic phase over aqueous phase. "All these challenges impede drug development, which has resulted in creating the gaps for finding cures for life threatening and rare diseases, and for unmet medical needs," says Shaukat Ali, PhD, Senior Director, Scientific Affairs & Technical Marketing, Ascendia Pharma, Inc.

These challenges span across all small and large molecules, and with more than 80% of new chemical entities (NCEs) belonging to BCS II and BCS IV, many of them cannot be developed due to lack of understanding of their physicochemical properties and inability to dissolve, says Dr. Ali. Small molecules are equally challenging because of their brick dust or being hydrophobic or lipophilic in nature, as well as their inability to disperse in aqueous solutions.

Driven by the large number of BCS Class II and IV therapies in the current pipeline and growing demand for effective therapeutics, the bioavailability enhancement services market is expected to grow at a steady pace.¹ Bioavailability is a key pharmacokinetic property that affects the ability of a drug to reach systemic circulation unaltered after administration. It is dependent on multiple factors, both physiological and drug related, such as solubility, pH, absorption area, permeability, and metabolism, as well as the route of administration. "Consequently, bioavailability can play an influential role in determining whether or not an active pharmaceutical ingredient (API) will be successful or fail during the early stages of drug development," says Sundeep Sethia, PhD, Head of R&D at Pii.



The solubility of drug formulations – both oral dosage and injectable – can be improved via the application of novel excipients (Roquette).

More than 75 bioavailability enhancement technologies are presently available in the market. Most (55%) support solubility enhancement, and nearly 70% provide bioavailability enhancement services for solids, followed fine particles/powders. Shifting focus of drug developers towards development of lipophilic drug compounds is anticipated to drive the demand for bioavailability enhancement technologies and services in the next 13 years. Consequently, the outsourced commercial demand for bioavailability enhancement is projected to increase.¹

This exclusive *Drug Development & Delivery* annual report highlights the services many of these outsourced providers offer to enhance solubility and bioavailability and get their clients' projects to market faster and cost effectively – while maintaining critical quality attributes.

Adare Pharma Solutions: Differentiation Through Enhancement

Since the advent of High Throughput Screening (HTPS) for lead identification, the volume of new compounds with poor aqueous solubility and/or bioavailability (BA) has been increasing phenomenally. This is because of HTPS's inherent inclination in identifying leads that are lipophilic in nature in order to favor target binding for efficacy. Even after multiple decades of pharmaceutical technological advancements, addressing solubility and BA issues of these drugs remains a difficult beast to tame for various reasons, says Srinivasan Shanmugam, PhD, Senior Director, Pharmaceutical Sciences, Business Support & New Technologies, Adare Pharma Solutions.

issues must primarily understand the underlying reasons for poor bioavailability and design the right formulation strategy to address the BA issue. In general, reasons for poor bioavailability are manifold, and could be one or more of the following: drug-related factors such as poor solubility; poor/slow dissolution/dissolution rate; poor permeability; and physiological barriers such as high first-pass metabolism and high efflux by Pgp. While drug-related factors constituting the Biopharmaceutical Classification System (BCS Class I-IV) determine drug absorption, physiological barriers dictate the ultimate BA of any drug. In other words, a drug with excellent solubility and permeability can achieve excellent absorption via gastrointestinal epithelium, however it could still be poorly bioavailable due to physiological factors like first-pass effect or efflux. Therefore, it is of paramount importance for formulators to understand both drug-related factors and physiological barriers when developing a viable formulation strategy. Additionally, knowledge of physicochemical properties of drugs — such as logP, melting point, and ionization — will be needed to select appropriate formulation strategy.

As far as formulation strategy, the BA of BCS Class II drugs can be enhanced either by improving their dissolution rate (Class IIa) or by enhancing solubility (Class IIb) via various formulation techniques such as particle size reduction, salt formation, surfactants, and amorphous solid dispersions. However, if poor BA is a result of permeability (Class III), then permeation enhancers or lipid formulations — including lipid-based solutions, suspensions, emulsions, lipid particles, and liposomes — can be used to improve the permeability. For drugs with solubility and permeability issues (Class IV), both strategies need

to be implemented. Finally, to address poor BA due to physiological barriers, lymphatic delivery and/or metabolic enzyme inhibitors could be a viable option to preclude first-pass metabolism, while the addition of Pgp inhibitor Pgp substrate drug will improve the BA.

Adare Pharma Solutions has demonstrated solubility enhancements of various drugs with traditional and enabled technologies. "Adare has increased the solubility of pH-dependent and poorly water-soluble drugs by creating acidic or basic micro-environments using organic acid or alkaline buffer with the help of our specialized Diffucaps® technology," says Dr. Shanmugam. "Additionally, another novel Adare technology platform, Optimum®, can create lipid microspheres and amorphous solid dispersions that enhance solubility and permeability of various BCS class drugs. Overall, Adare's technology can offer simple, fast, and efficient solutions for difficult-to-solve solubility problems. Most importantly, our expertise in development of easy-to-swallow and palatable patient-centric formulations with solubility/BA enhancement capabilities can deliver great value creation and differentiation for our clients."

Ascendia Pharma, Inc.: Non-Conventional Formulation for Better Design, Smarter Dosages

There is continued interest in finding new and innovative technologies for bringing NCEs to lead formulation optimization and further develop as potential drug candidates. The conventional approaches requiring pH adjustment, salt formation, complexation, and micronization all are well understood and used in many approved drugs with poor solubility. However, the continued trend of high melting



A scientist at Ascendia manufacturing long-acting injectable drug in a reactor.

drug candidates requiring medium to higher doses to meet the clinical end points means conventional formulations are less applicable. Therefore, non-conventional formulation technologies are highly sought to design better and smarter dosages to improve safety and efficacy of drug molecules.

Those approaches entail using polymeric excipients and solubilizers for preparation of amorphous solid dispersions by hot-melt extrusion, spray drying, co-precipitation, and Kinetisol®. On the other hand, some approaches require using

lipid-based excipients for preparation of dispersions such as self-emulsifying drug delivery systems (SEDDS/SNEDDS), and SLN and NLC lipid nanoparticles.

To overcome all these challenges, Ascendia has its patented proprietary solubilization technologies for addressing the solubility and bioavailability of new molecules and complex generics. Those include Nanosol®, LipidSol®, EmulSol®, and AmorSol® for tackling liquid/solid orals, parenteral, and topical formulations. “These technologies are aimed at handling small molecules as well as large

molecules like peptides and nucleotides,” says Shaikat Ali, PhD, Senior Director, Scientific Affairs & Technical Marketing, Ascendia Pharma, Inc. “Our manufacturing capabilities in sterile aseptic processing and lyophilization for injectable drug products employing one of the proprietary technologies bear the hallmarks of our state-of-the-art cGMP facility equipped with ISO 5 and ISO 7 cleanrooms.”

He says does point out that approaches for oral tablet versus oral liquid formulations differ considerably in terms of excipient selection, compatibility, storage of drug products, and the technologies used. “The molecules highly susceptible to food effects, having short half-life and first-pass metabolism, are difficult to develop by traditional dosage in oral tablets or liquids,” Dr. Ali says. In those cases, different strategies requiring the chemical modification, functional coating or core matrix selection have been used to delay the release.

Of course, for oral tablets, hot-melt extrusion, spray drying, co-precipitation with acceptable polymers and solubilizers are all widely used, but for liquid orals with poorly soluble molecules, solvent, co-solvents, lipids, and surfactants/solubilizers are often used for achieving the desired solubility and bioavailability. In liquid parenteral or injectable, however, the choice of excipients is different and more stringent from liquid orals. It is, therefore, important to select the parenteral excipients free of bioburden and endotoxins to minimize the safety risk and maintain a product’s critical quality attributes.

“Many drugs are unstable in liquid oral or parenteral dosage, thus, monitoring of their degradation and impurities could be important for long-term stability,” says Dr. Ali. “In such cases, if developing a parenteral drug, use of antioxidants, sta-

bilizers, complexing agents, and freeze drying or lyophilization could be better options to stabilize the drugs in powders for transportation, storage, and shelf life over extended periods. In others, sealed coatings of drugs with polymers or waxes are more relevant to minimize the API degradation, reduce the dose variabilities, and improve the performance of formulations.”

Candoo Pharmatech Company Inc.: Rational Formulation Design for Poorly Water-Soluble Drugs

As a technology-driven and customer-centric contract research, development and manufacturing organization (CRDMO) in Canada, Candoo Pharmatech specializes in advanced formulation solutions for small and large molecules and provides platform services to pharmaceutical companies.

Each molecule is unique in terms of its physicochemical and biopharmaceutical properties. Candoo integrates formulation expertise and modeling technique to evaluate the developability of compounds, identify the best-fit formulation technique, and allow clients to make informed decisions about their products. “Identification of the best-fit formulation strategy is critical to the successful development of poorly water-soluble compounds,” says Yongqiang Li, PhD, Co-Founder and CEO of Candoo Pharmatech Company Inc. “Moreover, applying readily deployable drug delivery platform technologies will accelerate IND-enabling and clinical studies.”

Candoo’s approach includes five steps: 1) establish a GastroPlus® PBPK model to incorporate physicochemical and biopharmaceutical properties of lead compound together with physiology of animal species; 2) perform a developability assessment for the compound, evaluate rate-

limiting factors for oral absorption, and predict food effect; 3) identify the best-fit formulation approach to maximize drug exposure and develop a bio-relevant dissolution method to check potential *in vivo* precipitation; 4) predict bioavailability profiles for ascending doses in human; 5) develop a practical formulation and scalable manufacturing process with Candoo drug delivery technologies.

“Candoo’s rational formulation design approach addresses the inherent challenges from compounds, shortens formulation development time, and avoids trial-and-error,” says Dr. Li.

Candoo applied its drug delivery technologies to help a pharma company develop four prototype formulations for a large animal study within one month. This was for a BCS II-neutral compound (low solubility, high permeability) with $\log P = 5.1$ and melting point at 139°C . Its solubility was less than $10\mu\text{g/ml}$ across physiological pH range. A PBPK model showed that the best-fit formulation strategy depended on the dose to be administered. Micronization of API ($D_{90} = 10\mu\text{m}$) was adequate for drug absorption if the human dose was less than 120mg, indicating that the dissolution rate was the absorption-limiting factor. In contrast, once the dose went beyond 120mg, amorphous solid dispersion or lipid-based self-emulsifying drug delivery system was needed to enhance bioavailability and reduce food effect. In this scenario, solubility became the major barrier for drug absorption. Dr. Li says that, based upon the insights gained from the PBPK model, Candoo developed four prototype formulations for the animal study and established a biorelevant dissolution method for *in vitro* drug release comparison. The animal study results enabled the client to rank these four prototype formulations and choose the

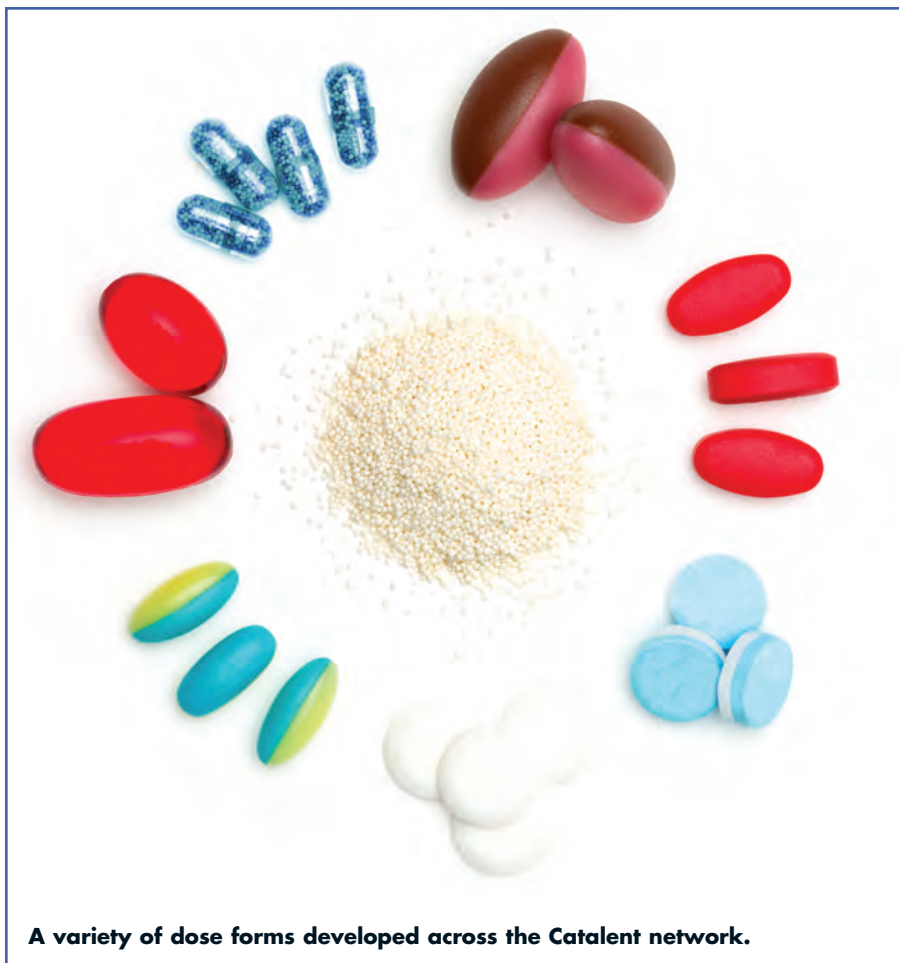
best-fit formulation for a clinical Phase I study.

Catalent: Formulation Approach Puts Clients on a Path to FIH Clinical Studies

The portfolio of small molecules coming out of discovery is expanding in terms of accessing new modes of action and targeting the molecular space for high potency. The focus on potency against a biological target has increased the “beyond the Rule of Five” (bRo5) molecules in the pipeline, and the FDA has approved 22 new oral bRo5 drugs, which account for 21% of new oral drug approvals in recent years.² These molecules often have poor drug-like properties and particularly low permeability, making it challenging to achieve the desired oral absorption profile. Thus, low oral bioavailability represents one of the main sources of inter-subject variability in drug plasma concentration, says William Wei Lim Chin, PhD, Manager, Global Scientific Affairs, Catalent.

Conventional approaches include particle-size reduction, API salt formation or isolating polymorphs, solid dispersion, and cyclodextrin complexation. There is no single technology that has universal applicability to every API displaying bioavailability issues, so each should be considered individually. The Developability Classification System (DCS) can help determine whether the molecule is dissolution-rate limited or solubility-limited for it to become systematically bioavailable, and provides insights into the appropriate formulation technology approach based on a drug’s classification.

Lipid-based drug delivery systems (LBDDS) offer an alternative method to enhance solubility. Within an LBDDS, an oil



A variety of dose forms developed across the Catalent network.

solution, self-emulsifying or self-micro emulsifying systems, and co-solvents mixture form part of the formulation with the API. Dr. Chin adds that APIs do not all behave the same way in the gastrointestinal (GI) tract. An API molecule contains different functional groups, which after oral administration, can be ionized or unionized depending on the pH variation along the different parts of the GI tract, in turn affecting drug absorption. For permeation-limited molecules, LBDDS may be beneficial as certain lipid excipients and surfactants can promote permeation of the drug in the GI tract. The digestible lipid excipients in an LBDDS enable the drugs to navigate the GI tract in a natural digestion and lipolysis process.

Dr. Chin recommends specific best practices for formulators dealing with solubility and bioavailability issues. He says to establish whether the bioavailability

issue is related to solubility, permeability or both, appropriate modeling tools, both *in silico* and *in vitro*, coupled with targeted preformulation and analytical testing, can help determine the issue(s). The correct formulation strategy can then be identified and implemented based on a working understanding of the appropriate critical physicochemical properties.

At Catalent, customers' issues tend to revolve around the limited amount of available API of a poorly soluble drug. Dr. Chin explains that after a comprehensive developability assessment of the molecule, a formulation approach will be recommended along with essential preformulation characterization, such as small-scale micro-dissolution testing, which works with very small amounts of material. Permeation testing with a Caco-2 cell line may also be recommended to understand transport across the epithelial cells of the

gut and any efflux effects, which again requires small amounts of material.

"Together, these data provide powerful leverage into understanding the likely exposure, and support physiologically-based pharmacokinetic modeling to rule out the first-pass effect, and to predict human exposure," he says. "This assessment recommends a formulation approach with a comprehensive path forward to reach toxicology and pharmacokinetic studies, and ultimately, first-in-human clinical studies."

Cyclolab Ltd.: Cyclodextrin Formulations Enhance Ophthalmic Drug Delivery

Cyclodextrins (CDs) are mostly used in oral and injectable drug delivery for improving solubility or chemical stability of lipophilic drugs, but CDs can solve problems in other routes of administration as well. Ophthalmic drug delivery is one of the most challenging areas for pharmaceutical scientists. The ocular bioavailability via eye drops is very poor, usually lower than 1%, mostly due to the precorneal loss related to drainage, tear turnover, short residence time, and the impermeability of the cornea, explains Dr. Zoltan Fülöp, Senior Formulation Scientist, CycloLab Ltd.

"Furthermore, the administered volume with one drop is somewhere between 25 and 70µl, thus, it is required to maximize the concentration of the drug close to and beyond the physical limits," he explains.

Currently only a handful of marketed eye drop formulations contain cyclodextrins: hydroxypropyl betadex (HPβCD) is used with indomethacin, levocabastin, and azelastine; hydroxypropyl gamma cyclodextrin (HPγCD) is used with diclofenac and olopatadine; and randomly methy-

lated beta cyclodextrin (RAMEB), is used with chloramphenicol. Other formulations are visible on the horizon, says Dr. Fülöp, such as a reproxalap eye drop with Betadex sulfobutyl ether sodium (SBECD) and a dexamethasone suspension eye drop with Gammadex (GCD). He says: "CDs are utilized as solubilizers in the case of HPBCD, RAMEB, and SBECD, allowing solution eye drop formulations with APIs where only suspension or emulsion formulations were possible before."

He adds that HPGCD is selected due to its compatibility to benzalkonium chloride, and GCD is special due to its ability to form nano- and microparticulate aggregates. CDs also can act as permeation enhancers, providing an elevated drug concentration on the membrane barriers (cornea and conjunctiva). Although CDs cannot cross these barriers (due to toxicity), they can interact a little with the corneal surface, and the complexed drug molecules can permeate into the cornea from the CD cavity. CDs can maximize the permeation of the dissolved drug molecules if the drug concentration on the membranes is close to saturation concentration. The residence time of a CD formulation can be either improved by using viscosity enhancers and gels or CDs can be used in a novel way to form particles that take time to fall apart, as in the case of GCD. Specialized CD-containing formulations can even deliver the drug to the back of the eye, which in the future could replace invasive therapies such as intravitreal injections or implants with a simple eye drop formulation and treat retinal diseases in a patient-friendly manner, says Dr. Fülöp.

"We encourage formulation scientists of pharmaceutical companies to consider CDs in the design of new ophthalmic formulations, as they provide a safe and pa-

tient-friendly solution to make new products available of poorly soluble drugs and improve bioavailability up to the point where they can deliver drugs to the back of the eye," he says. "Based on our experience in early-stage drug product development, we expect to see more SBECD and HPBCD eye drop developments in the future, as these safe excipients have great potential and are already recommended by the EMEA."

Evonik: Solutions Enable Molecules to Become Oral Drugs Where Not Previously Possible

Although there have been many advances in terms of solubility enhancement in the past few years, new molecules are more complex, requiring sophisticated approaches. Amorphous solid dispersions (ASD) technologies are often used to enhance small molecule solubility. But this approach is not always feasible if molecules are sensitive to high temperatures, mechanical stress or are poorly soluble in suitable organic solvents, says Kamlesh Oza, Technical Sales and Formulation & Application Services North America, Evonik.

Developers of recently emerging biopharmaceutical therapies are looking for

new technologies to address bioavailability challenges. These biopharmaceuticals are normally more effective when delivered in specific target areas of the gastrointestinal tract, which means they need to be protected from gastric juices. However, many are too sensitive for a regular coating process. "These challenges, among others, need to be addressed on ever more restricted timelines, which is why solubility enhancement remains an exciting challenge," he says.

One of our Evonik's solutions for small molecules is based on a new technology that allows scientists to obtain an ASD through a gentler, emulsion-based process. This technology processes an API under low temperatures and low mechanical stress and then engineers the final particles to obtain a uniform, free flowing, highly concentrated ASD powder, which can be tableted or filled into capsules. This particle-engineered ASD can also improve pharmacokinetic performance by precisely controlling particle size and shape, which, consequently, also improves scalability. "This latest innovation addresses some tough solubility problems that cannot be solved with conventional technologies and therefore fulfills an unmet need for our pharma partners," says Dr. Oza.

Another Evonik advancement effi-



One of Evonik's solutions processes an API to obtain a highly concentrated ASD powder that can be tableted or filled into capsules.

ciently improves bioavailability for biologicals or microbiome therapies, for drugs needing protection from an acidic environment. The technology is a gastric-resistant, empty coated capsule based on extensive enteric coating experience. The robust enteric capsules can be tailored to target a specific gastrointestinal site. "They significantly improve the bioavailability of biologics without exposing them to moisture and heat in a regular coating process, thus allowing a wide range of formulations," he says.

Both solutions described are fully adaptable from early pre-clinical to late commercial stage. Dr. Oza concludes: "We are confident that these innovations will enable the use of new molecules that previously could not be formulated as oral drugs."

Gattefossé: Choose a Platform That Fits the Drug

Many new compounds being developed sacrifice solubility for potency, leading to an increased need to take a potentially highly efficacious drug and improve its solubility as well as absorption characteristics, says Andrew Schultz, MS, Sales Manager, Pharmaceutical Division at Gattefossé.

"The biggest advances to aid solubility and bioavailability have come from our ability to develop predictive *in silico* models and biorelevant *in vitro* methods, which help reduce development lead times and help give us the best chances for success," he says. "For instance, the historically used *in vitro* dissolution testing in aqueous media is inadequate for evaluation of lipid formulations. Dissolution testing in the presence of digestive enzymes (lipolysis test), on the other hand, is a more effective

way of anticipating the lipid formulation performance."

Mr. Schultz says that it is extremely important to determine why a compound is not showing good bioavailability. There could be barriers aside from a lack of aqueous solubility that need to be understood and that could help steer formulation development to overcome these hurdles. These may include poor permeability across the enterocytes or pre-systemic elimination. In such cases, the drug may benefit from formulation with long chain fatty acid esters that are known to avoid hepatic elimination, or the addition of short chain fatty acid esters that enhance permeation by transient opening of tight junctions, he says. An equally important consideration is the commonly encountered food effect, requiring lipid-based or other systems to overcome this effect.

"We run into this all the time with clients who have poorly soluble actives and found little success with the commonly available techniques such as amorphous spray dried dispersions, co-crystals, micronization, and pure solvent use to solubilize NCEs," says Mr. Schultz. "The key is to choose a platform that meets the specific challenges of the drug, not to attempt to force a drug's characteristics into a technology. In our experience, using lipids in a systematic formulation approach is one of the best ways to improve bioavailability and can help streamline the formulation effort. When the enabling platform matches the true needs of the API, success rates are higher. And, if selected correctly, a single formula may be used for early-stage pK development through commercialization."

Ligand Pharmaceuticals: Solubility-Enhancing Excipient Opens New Routes of Administration

Ligand Pharmaceuticals has seen a steady stream of inquiries for how Captisol® (sulfobutyl ether beta cyclodextrin) can help with solubility/bioavailability and stability of active pharmaceutical ingredients. There are currently at least 60 products in development pipelines around the world using Captisol for formulation enhancement.

"Another indication that APIs continue to need assistance in solubility improvement is the increased demand for Captisol and the number of product approvals containing Captisol expected in 2023-2024," says Vince Antle, PhD, Senior Vice President of Technical Operations & Quality Assurance at Ligand. "Upcoming product approvals open the door to the use of Captisol in new routes of administration, namely oral, ocular, and subcutaneous. In addition, one of the anticipated product approvals is targeted for a pediatric demographic."

J.D. Pipkin, PhD, Vice President of New Product Development at Ligand, says that formulators know that best practices for dosage form development of poorly water-soluble compounds depend largely on the physical/chemical characteristics of the API, route of administration, indication, and whether the drug will be given on an acute or chronic regimen. "Keeping the formulation as simple as possible is usually the best strategy from both a product and regulatory standpoint," says Lian Rajewski, PhD, Senior Research Investigator at Ligand. "Typically, the fastest way to move through the development process, is to use safe, well-established, globally accepted excipients. Captisol is a solubility-

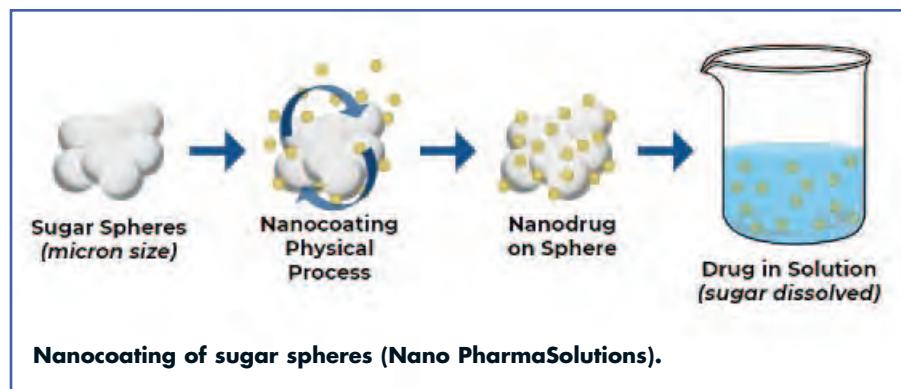
enhancing excipient (derivatized cyclodextrin).”

For formulations using cyclodextrins, the first step is to assess the structure and physicochemical properties to determine if the molecule is a good fit for using a cyclodextrin technology. Then, evaluate the interaction of the compound of interest and the cyclodextrin. Additional parameters such as pH adjustment, other enhancers or processing techniques may be used to achieve the desired dosage form characteristics. Further understanding of the phase solubility space is essential to identifying the final formulation for a successful product.

Nano PharmaSolutions, Inc.: Single Nanoformulation for All Phases with No Chemical Additives

Poor solubility remains one of the greatest challenges in pharmaceutical development. More than 70% of new chemical entity (NCE) candidates have poor solubility and thereby bioavailability, resulting in the leading cause for the failure of Phase 1 First-in-Human (FIH) trials. While the number of methods for enhancing drug solubility continues to increase, trade-offs in cost, development time, and formulation bridging animal and PK studies prove finding an optimal solution elusive.

Chemical modification to create salt forms or co-crystallization requires excipients to enhance solubility, which offer little to no therapeutic benefit; and even pose health hazards at certain levels. Solid dispersion by spray drying or hot-melt extrusion requires lengthy polymer excipient screening steps and has its limitations. Nanoformulation offers an attractive alternative to enhance solubility and bioavail-



ability, says Kay Olmstead, PhD, MBA, CEO, Nano PharmaSolutions. However, nanoformulation is not widely utilized in early drug development of solid oral formulation due to fears of long development time and poor flow characteristics of sub-micron size drug particles.

NanoTransformer™ is a scalable nanosizing technology that generates drug nanoparticles in the 200-600nm (D50) range. This process uses gentle heat and reduced pressure to evaporate solid API to gas phase, which then gets deposited on commonly used hydrophilic granulation excipient (e.g., mannitol, starch or microcrystalline cellulose) as nano-granules with drug nanoparticles deposited on the drug excipients. Drug loading through this process can be as high as 25-30% in some examples. These nano-granules may be used for animal safety studies as aqueous suspension, for FIH clinical trials as powder-in-capsule or powder-in-bottle, and as compressed tablets for later stage clinical trials, all without changing the base formulation, explains Dr. Olmstead. Using the same nano-granulation as the intermediate of oral dosage form in FIH and Phase II/III clinical trials removes the need for a bridging PK study required by the regulatory agencies for enhanced formulation development after completing a FIH trial. Solvent-free nanoformulation for animal safety studies will lessen the risk of

FIH clinical challenges due to formulation changes between the phases.

The NanoTransformer granulator is a retrofitted industrial vacuum nano-coater, which is commonly used in semi-conductor and aerospace industries, enabling the production of drugs under cGMP conditions. “The development time for nanoformulation is rapid and requires very little API, which suits preclinical studies well. Vacuum coaters can generate hundreds of kilograms of nanoparticles, therefore scaling up to production-sized batches is achievable,” she says. GMP manufacturing of clinical supplies for nano-granulation will be available starting late 2023.

She adds that NanoTransformer™ vacuum-generated nano-granules prove to be chemically and physically stable and easy to handle. Surface-area-to-volume can be up to a 1,000-fold increase, thereby improving dissolution according to the Noyes-Whitney equation. The *in vitro* dissolution itself can see an increase of 4-5x, leading to an increase of up to 500% or more bioavailability for many APIs. In tandem with higher solubility and bioavailability, nano-granulation also enables API to be further formulated into various dosage forms, including liquid or solid oral, ocular, intranasal, dry powder inhaler and injectable, allowing for optimal delivery for various therapeutic applications.

Pii: Formulation Approach Results in 100-Fold Increase in Bioavailability

Bioavailability is an important factor to consider when evaluating the efficacy of drug products. The global biopharmaceutical industry is witnessing a rapid increase in difficult-to-develop drugs with low solubility and/or permeability. As this trend persists, there will be a surge in need for technologies that facilitate bioavailability enhancement. Innovation is key in developing better technologies and methods; current approaches may not be adequate to meet the ever-increasing complexity of pharmacological interventions and novel drug classes. These technologies are broadly classified into three main categories: physical, chemical, and biological. Each of these methodologies has its advantages and limitations. But, regardless of the approach taken, technologies must be advanced to ensure that drugs can reach their target sites efficiently. Developing a formulation plan should first include an understanding of the physicochemical properties of the drug, the required dosage form and selection of appropriate excipients/technologies to evaluate in a step by step approach, while keeping in mind the pharmacological properties that may be a factor once dosed.

"Without solubility and bioavailability, desired drug concentrations cannot be attained, leading to failure of drug efficacy," says Sundeep Sethia, PhD, Head of R&D at Pii.

Knowing this risk, many pharmaceutical companies now prioritize bioavailability enhancement when developing their product candidates, thus allowing for optimal quantities of bioactive compounds at the target site of action. "The influx of the new active molecules that are primarily insoluble in an aqueous environment,

and the introduction of relatively few new pharmaceutical excipients providing solubilizing potential, has kept solubility/bioavailability a major challenge in drug formulation," he says.

He adds that bioavailability and systemic/local absorption and distribution of therapeutic interventions are intertwined, as bioavailability affects the degree to which drug concentration can be maintained in the body. Technologies available today for improving solubility include particle size engineering via dry powder micronization or nanosuspension; crystal structure disruption to provide solid dispersions using various technologies such as melt agglomeration, drug layering onto pellets, and spray drying; use of functional excipients like cyclodextrins to form inclusion complexes with the drug or surfactants/co-surfactants to form SEDDS, SMEDDS or SNEDDS *in vivo*. All of these have potential for providing higher bioavailability.

The mode of administration is also an important factor that can influence drug bioavailability or the percentage of the drug entering systemic circulation in humans. Intravenous injection offers the highest level of bioavailability with 100% availability of the introduced drug, while other available routes provide lower rates. "Studies have found that physical form also plays a role in the absorption rate of drugs; those released in gas form will be absorbed more quickly than liquids that are more quickly absorbed than solids," says Dr. Sethia. "Thus, it is essential to consider mode and form when choosing a medication route for effective uptake by the body."

Pii's clients bring various compounds to the CDMO that exhibit several reasons for lacking solubility and/or bioavailability. In one case, Pii was tasked to improve

the solubility and bioavailability of a hydrophobic compound. To address these concerns, various approaches were utilized. Solubility and complexation studies were performed to optimize the formulation to increase the solubility. Using the Inclusion Complex formulation approach, a select cyclodextrin provided promising solubility and physical stability, explains Dr. Sethia. Also, a SEDDS approach combination of oil and polymers that included surfactant/co-surfactant and emulsifier was proposed. "Stable formulations using both approaches provided greater than ten-fold increase in drug solubility," he says. "A bioavailability study comparing the suspension lipidic vehicle in a soft gel dosage form versus neat API resulted in an increase by 100-fold in bioavailability."

Quotient Sciences: Unlocking the Potential of Each Molecule

The pharmaceutical industry has a healthy pipeline of promising new chemical entities (NCEs), however development is still constrained by solubility and bioavailability challenges that increase formulation complexity, raise failure rates, and drive-up development costs. This remains a prevalent issue because molecules are progressing too quickly into downstream product development without being properly assessed and understood in the preclinical and candidate selection stages, contends Dr. Dolly Jacob, Director of Integrated Development Services, Quotient Sciences. "Drug developers utilizing the traditional formulation development model aren't assessing a molecule's developability before pressing ahead into development or using key biopharmaceuticals tools that can greatly aid in ensuring a molecule's success, thus creating an industry need for a new and innovative way to

develop drugs more efficiently.”

For smooth transition of an NCE from candidate selection into First-in-Human (FIH) and onward into Proof-of-Concept (POC) and beyond, Quotient Sciences employs an integrated approach, combining a robust biopharmaceutics, physiochemical, and DMPK package, with appropriate *in silico* and *in vitro* modelling tools to aid formulation design and clinical flexibility. “This novel approach, known as Translational Pharmaceutics®, allows us to respond to emerging *in vivo* clinical performance data that aids in critical formulation decision making and improves the likelihood of both downstream clinical and commercial success,” says Dr. Jacob. “This approach enables formulations to be designed, manufactured, and clinically evaluated under a single organization. Data from the early stages of the clinical evaluation can be fed back into the process, allowing formulations to be adjusted, manufactured, and passed straight into the clinic again. This unique approach means that formulation issues can be detected, corrected, and clinically validated more quickly.”

Some strategies used for clinical predictions include Biopharmaceutics Classification System (BCS) and Developability Classification System (DCS) assessments, biorelevant characterization, precipitation experiments, solid-state characterization, and *in silico* predictions. “These strategies, in combination with integrated processes and development models, simplify the outsourcing paradigm, enabling reduced timelines, risks, and costs for our customers,” she says.

By understanding the drivers of poor solubility and permeability of a drug, formulation efforts can be focused on the correct development techniques to provide meaningful improvements in *in vivo* per-

formance. For example, Quotient Sciences utilized its integrated platform, Translational Pharmaceutics, to rapidly identify and overcome solubility and bioavailability challenges for one of its clients. The customer had a BCS II molecule with preclinical data, suggesting that solubility may limit exposure. “Utilizing our integrated platform, we designed a three-part single ascending dose (SAD) and multiple ascending dose (MAD) study for a program that provided formulation flexibility and quickly identified a drug product format that was suitable for Phase II (POC),” explains Dr. Jacob. “Using a unique formulation design space, in addition to the FIH primary objectives of safety and tolerability, we employed exquisite precision in dose escalation, screening multiple formulations and dosage form bridging at a particular SAD dose stage based on real-time emerging data.”

Quotient Sciences developed five formulations: a micronized tablet, a lipid formulation, two spray-dried dispersion intermediates, and a tablet formulation using the spray-dried dispersion. In this three-part study, it was possible to integrate the assessment of solubilization technologies all within a single clinical protocol to enable identification of a drug product suitable for Phase II POC, removing the need to conduct larger scale, cost-prohibitive process development and lengthy stability programs for multiple technologies, she explains.

“Our Translational Pharmaceutics platform allowed us to identify a spray-dried tablet formulation to take into the next phase,” continues Dr. Jacob. “The time taken from development program start to final pK delivery was 18 months, which would typically take an average 46 months using a traditional formulation development model. By employing an inte-

grated approach for this program, we were able to reduce the time and cost of early drug development for our customer, while maximizing the probability of success in getting their molecule to patients faster.”

Roquette: Exploring the Feasibility of a Solubility Enhancer in Lorazepam Formulations

As a provider of excipients, including cyclodextrin, Roquette understands that the solubility of drug formulations – both oral dosage and injectable – can be improved via the application of novel excipients. Cyclodextrins, in particular, are showing significant promise as solubility enhancers in oral as well as parenteral delivery formats, where they have been demonstrated to improve the solubility and bioavailability of small-molecule formulations, in addition to enhancing chemical and physical stability.³ Importantly, they are already approved for oral and parenteral delivery – and thus suitable for vaccine development and oral solids, says Olaf Häusler, Global Technical Application Scientist, Roquette.

“In both delivery systems, the desired outcome is better solubility and higher absorption,” he says. “Cyclodextrin excipients can support both these effects. The hydrophobic interior of the molecule forms a complex with the insoluble drug compound, encapsulating it, while the hydrophilic exterior forms hydrogen bonds with aqueous solvents, forming a solution. This helps to increase the absorption of oral and parenteral formulations containing a hydrophobic compound.”

Roquette’s hydroxypropyl beta-cyclodextrin (HPβCD) solution – KLEPTOSE® – has demonstrated benefits as a solubility enhancer in lorazepam formulations – a BCS Class II drug commercially available

as a solid and liquid dosage form. Traditionally, the drug's parenteral formulations are administered as a solution in polyols, Mr. Häusler explains. However, this can create serious patient compliance issues.

"We explored the feasibility of a parenteral alternative using lorazepam solubilized by cyclodextrin⁴," he says. "Our investigation found that HP β CD significantly enhanced the solubility and stability properties of lorazepam, making it a viable manufacturing formulation that addresses patient compliance by eliminating the side effects observed with organic solvents."

The Solubility Company: Proprietary Tech Elicits Solubility Data from Microscopic Amounts of Substance

As novel drug delivery tools and technologies keep expanding the boundaries of oral product development beyond the Rule of Five, compounds are increasingly prone to solubility issues, says Sami Svanbäck, PhD, CEO, The Solubility Company.

"Over the past two decades, addressing poor bioavailability has become an interdisciplinary task between stakeholders in drug candidate selection, lead optimization, and drug product development," says Dr. Svanbäck. "The increase in the number of approved new drug products with molecular properties beyond the Rule of Five is explained by incremental and concurrent advances in analytical technologies, molecular biology, target di-

versity, drug design, medicinal chemistry, predictive modeling, DMPK, drug metabolism and pharmacokinetics, and drug delivery."

He adds that lipid-based formulations, in particular amorphous solid dispersions, are leading the trend in novel oral drug delivery technologies reaching the market, with approvals of novel and advanced excipients tailored to specific applications facilitating this trend. The starting point for all development is, however, a broad and deep understanding of the molecular properties such as solubility in conditions relevant to the drug's ability and developability of the NCE. Novel analytical tools working on the small sample amounts available in discovery and early development phases are driving the advancement in early informed decision making.

The Solubility Company's proprietary Single Particle Analysis (SPA[®]) technology, based on machine vision and AI, produces solubility data from microscopic amounts of substance. Services include measurement in aqueous media, biorelevant media, formulation vehicles, lipids, and organic solvents.

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The advertisement also features several overlapping magazine covers with titles such as 'Self-Injection: the "New Normal"', 'Injection Device Trends', 'The Promise of siRNA Therapies', and 'Analytical Testing Trends'.

Drug Development EXECUTIVE



Gil Efron

Chief Executive Officer

Purple Biotech Ltd.



Purple Biotech Ltd.: Developing First-In-Class Oncology Therapies

Purple Biotech Ltd., headquartered in Rehovot, Israel, is a clinical-stage company developing first-in-class oncology therapies that seek to overcome tumor immune evasion and drug resistance. The company's pipeline includes CM24 and NT219. The company is advancing CM24, an mAb that targets CEACAM1, an immune checkpoint protein that allows tumors to evade the immune system; it is evaluating CM24 in a Phase 2 trial as a combination therapy with the PD-1 inhibitor nivolumab and chemotherapy for metastatic pancreatic cancer. This study is conducted in clinical collaboration with Bristol Myers Squibb. NT219 is a novel small molecule dual inhibitor targeting two critical tumor-resistance pathways; the company is currently advancing it in a Phase 1-2a trial as monotherapy treatment and in combination with cetuximab for various solid tumors. Purple Biotech recently acquired Immunorizon Ltd., a private company developing multi-specific T and NK cell engagers that selectively activate the immune response inside the tumor microenvironment. The acquisition provides Purple Biotech with an expanded portfolio of investigational tri-specific antibody compounds that target multiple tumor antigens, the first being 5T4, and offer the potential to further expand to additional targets.

Drug Development & Delivery recently interviewed Gil Efron, Chief Executive Officer of Purple Biotech, to discuss the company's focus on identifying and developing promising molecules that may offer first-in-class approaches to treating devastating cancers with large unmet medical needs.

Q: What is your approach to finding existing molecules, whether small molecules or biologics, that may offer new therapies for intractable cancers that are difficult to treat under current standards of care? How do you uncover the hidden potential of these promising compounds?

A: The world of biotech and pharmaceutical research is replete with investigational assets that have not yet been funded for the clinical trials needed for regulatory submission or even to establish clinical proof-of-efficacy. Purple Biotech sees enormous opportunity with some of these “hidden gems,” and focuses on identifying, in-licensing, and developing promising and innovative oncology assets. We thoroughly vet the potential of these assets through our own research, engagement with other companies and laboratories, and the insights of our external advisors. We seek assets that are potentially first-in-class approaches to solving major unmet medical needs in cancer treatment and that offer synergies with other molecules in our portfolio and synergy with our capabilities. Our commitment to truly innovative approaches is nicely illustrated by CM24 and NT219, two clinical-stage, first-in-class drugs being developed to treat some of the world's most devastating cancers. Additionally, our recent acquisition of the innovative, first-in-class tri-specific oncology assets will create synergies with our existing assets and broaden our pipeline.

Q: Can you explain the transition from Kitov Pharma to Purple Biotech? Why did the company shift its focus to first-in-class oncology therapeutics?

A: During December 2020, Kitov Pharma Ltd. announced it was changing its name to Purple Biotech Ltd. and its stock began trading on the NASDAQ and TASE exchanges as PPBT. This name change signaled the completion of a transition that reflected a corporate decision to focus resources on developing innovative oncology assets targeted at difficult-to-treat cancers with high unmet medical needs. The excitement of clinically developing potential first-in-class therapies for such cancers was reinforced by the acquisitions of CM24, a novel mAb targeting CEACAM1, an immune checkpoint molecule that supports tumor immune evasion and survival through multiple pathways, and NT219, a novel small molecule dual inhibitor of IRS and STAT3, two molecular targets known to be associated with resistance to inhibitors of the MAPK pathway. At Purple Biotech, our clinical development efforts initially seek the most efficient

path to clinical proof-of-concept before expanding to additional indications or product combinations, based on clinical evidence. This strategy allows us to stratify our disease targets efficiently and streamline clinical development of investigational compounds that would benefit as broad a set of patients as possible.

Q: How does CM24 restore the ability of patients' immune systems to invade and kill solid tumors, preventing metastases? What is unique about CM24's mode of action?

A: CM24 targets CEACAM1, a well-recognized immune checkpoint protein that lowers the ability of the immune system to kill cancer cells. CM24 facilitates immune system access to tumors by unlocking CEACAM1's checkpoint mechanisms that prevent T cells and “natural killer” (NK) cells from attacking and destroying cancer cells. Because CEACAM1 is over-expressed on multiple types of solid tumors, CM24 may provide a way to turn off this tumor defense mechanism in several oncology disease states. We are currently partnered with Bristol Myers Squibb in a Phase 2 trial to investigate the use of CM24 in combination with nivolumab to treat metastatic pancreatic patients who express high levels of CEACAM1. In addition, we believe CM24 can also contribute to reducing metastases by blocking adhesion of cancer cells to CEACAM1 expressed on neutrophil extracellular traps, and we are hopeful that strong proof-of-concept data against CEACAM1 in metastatic pancreatic cancer will support investigations of other cancer therapies.

Q: What is NT219, and why are you excited about its development?

A: Cancer cells have a challenging ability to activate bypass mechanisms that allow them to escape therapeutic agents. NT219 is a first-in-class dual small molecule inhibitor of two mechanisms of drug resistance, IRS1/2 and STAT3, two common resistance pathways that are present on many solid tumors and which drive tumors' resistance to many cancer drugs (such as inhibitors of EGFR, BRAF, MEK, and KRAS). By creating effective resistance to cancer therapies, IRS1/2 and STAT3 fuel cancer growth and hamper the long-term benefit of approved cancer drugs. In early research, NT219 has shown itself able to disable these bypass mechanisms, thereby allowing cancer drugs to

continue working. NT219 is the only dual inhibitor of these two resistance pathways, and we have shown the concomitant inhibition of both targets is required to restore the treatment efficacy of standard-of-care therapies. We are pursuing clinical trials to determine whether and how NT219 can be combined with existing oncology drugs to shut down the resistance pathways that limit and eventually halt the drugs' efficacy. NT219 is currently being investigated in a Phase 1/2 clinical trial in combination with cetuximab to evaluate its effectiveness in treating recurrent/metastatic head-and-neck squamous cell carcinoma (SCCHN) as well as for its potential use as a monotherapy in multiple tumor types. Successful proof-of-concept data from this trial may hold promise for research into potential combination treatments for other types of solid tumors.

Q: There has been discussion of a potential application of NT219 as an effective adjunct to therapies targeting KRAS mutations in non-small cell lung cancer (NSCLC). Can you explain what is going on?

A: If approved, NT219 will be a valuable adjunct to approved cancer drugs by disabling the molecular processes that allow resistance to develop during treatment. This may be relevant to one of the most widely discussed and promising treatments for several cancers – KRAS inhibitors, drugs that target mutations of the cell-signaling KRAS oncogene that drive tumor growth and allow cancers to flourish. Sotorasib (Lumakras®, Amgen) was approved in May 2021 followed by adagrisib (Karazati®, Mirati) in December 2022 to tackle a specific KRAS mutation (G12C) present in a significant fraction of NSCLC patients. Numerous other compounds are in clinical trials for the same molecular target. Unfortunately, patients on these KRAS inhibitors have seen early relapse and a limited survival benefit, suggesting that combination approaches will be required to eventually break this deadlock. No other treatment is available for all other KRAS mutations, other than the G12C mutation.

Our research as well as several recent publications indicate one of the primary ways mutated KRAS genes escape these drugs and develop resistance is via IRS1/2, one of the molecular pathways that NT219 effectively shuts down. Our hypothesis is that NT219, if given in combination with KRAS inhibitors, could greatly improve the KRAS inhibitors' effectiveness and strengthen the clinical impact of drugs such as sotorasib or adagrisib, thereby prolonging patients' lives. In data we reported from our clinical studies, we saw a partial response in a mutated KRAS patient as well as stable disease in multiple patients who also

had KRAS mutations. We are looking into these data and evaluating the potential treatment of this patient population with NT219.

Q: In addition to the clinical development of your two current assets, CM24 and NT219, do you have other irons in the fire? Where do you see Purple Biotech heading in the next 2 to 3 years?

A: Within 2 to 3 years, we would hope to have a proof-of-efficacy for CM24 to treat late-stage pancreatic cancer in combination with nivolumab and standard-of-care therapy. If CM24 gains such proof-of-efficacy and subsequent FDA approval, it would be a first-in-class therapeutic targeting CEACAM1. Additionally, NT219 is showing very promising early clinical efficacy results and will, we hope, show proof-of-efficacy in at least one combination therapy targeting difficult-to-treat cancers.

The portfolio of tri-specific antibodies that we recently acquired is a perfect illustration of our strategy to invest in innovative biologics and to expand our pipeline with additional preclinical programs. This new technology is differentiated not only by the combination of the NK and T cell engagement but also by the conditional activation at the tumor microenvironment, which we believe provides an opportunity for better therapeutic outcomes for patients. We also believe there is a potential synergy between this new technology and our current drug candidate CM24, as well as with the knowledge and expertise we have gained over the years through both preclinical and clinical development. We expect to advance the first of the newly acquired assets to an IND submission in approximately two years.

Beyond CM24, NT219 and our newly acquired multi-specific assets, we are exploring with biotech companies and academic research centers about other promising drug candidates we could in-license and develop; in some cases, we may opt to develop commercial partnerships with other companies whose focus is synergistic with our own. And finally, we continue to engage with the investment community to deepen their understanding of the value of Purple Biotech. We are building a robust investor and analyst base, and it is our hope to accelerate this process moving forward. ♦

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DELIVERY TECHNOLOGY

NeuroDirect™ Ketamine: Novel, Non-Systemic Topical Therapy for PTSD & Associated Intractable Depression

By: Ronald Aung-Din, MD, and Chantelle G. Martin, MBChB

INTRODUCTION

PTSD, Post-Traumatic Stress Disorder, is a brain memory processing disorder that continues to affect emotions, thought processes, and behaviors such that normal functioning becomes difficult, if not impossible, in affected individuals. Many, particularly war veterans, resort to suicide as a means to escape its overwhelming effects.¹⁻⁵

Patients with PTSD have in common experiences with profound associated psychological stress that remains embedded in their memory and continues to playback in various ways, influencing their mental well-being and functioning. There may also be associated physical aspects to the event that contribute to the process, such a sexual assault, physical abuse, head injury, or other trauma. But most important are the emotionally traumatizing aspects of the event that remain unresolved in the affected person's psyche.⁶⁻⁷

Symptoms of PTSD are varied, and pharmaceuticals are generally used to specifically treat them. Counseling and bio-feedback are also used as augments. Symptoms may include flashbacks and uncontrollable thoughts about the event, nightmares, and severe anxiety. PTSD symptoms are generally grouped into four types: intrusive memories, avoidance, negative thinking and mood, or changes in emotional reactions.^{1,4,8,9}

Although medications benefit in reducing PTSD symptoms, no single effective drug treatment for PTSD exists. Positive symptoms, such as re-experiencing, hypervigilance, and increased

arousal, respond better to medication than negative ones of avoidance and withdrawal. As residual symptoms in spite of medications are the rule, much research continues in PTSD symptom management.¹⁰⁻¹²

SSRIs (selective serotonin reuptake inhibitors) have been considered first-line drug treatment. Data exists to support use of the following SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Bupropion and the SNRI venlafaxine have the lowest patient drop-out rates due to medication side-effects.¹³⁻¹⁷

In addition to antidepressants and benzodiazepines, anti-convulsants and other non-traditional compounds have been used in treating PTSD symptoms. Commonly used anticonvulsants include Carbamazepine, Topiramate, Lamotrigine, and Valproic Acid, which help reduce mood swings, agitation, impulsivity, and aggression. Narcotics and opioids are used for physical pain related to physically traumatic events.¹⁸⁻⁴⁰

From the above, it is apparent the majority of patients with intractable symptoms of PTSD are on several different medications or "poly-pharmacy." Not only are symptoms not adequately relieved, but side effects and drug-drug interactions can be problematic. This has led many patients to self-medicate with alcohol, cannabis, and off-the-street narcotics and psychedelics. Psychedelics include LSD, psilocybin ("magic mushrooms"), cocaine, and ketamine ("Special K.").⁴¹⁻⁴⁵

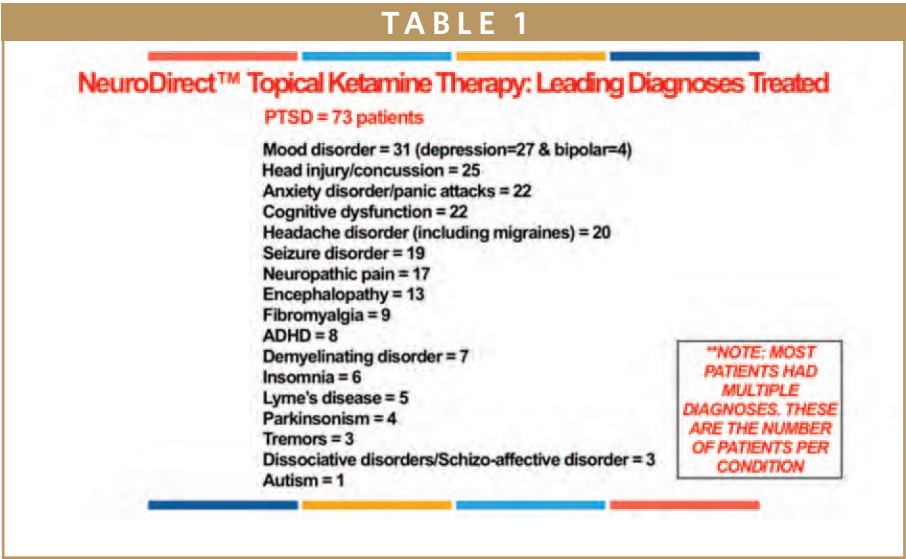
Ketamine was primarily developed for induction and maintenance of general anesthesia. It induces “dissociative anesthesia,” a trance-like state providing pain relief, sedation, and amnesia. It is distinguished from other general anesthetics in that respiratory functions are preserved. Cardiac status is unaffected with maintenance of normal blood pressure, making it ideal for traumatic situations with significant blood loss and circulatory compromise. It was extensively used for battlefield surgical anesthesia in the Vietnam War.

Ketamine was first synthesized in 1962 and approved in US in 1970. It has been regularly used on dogs and horses; therefore, called “horse tranquilizer.”⁴⁶ Because of its safety profile, it is used in pediatrics.

At lower, sub-anesthetic doses, ketamine has shown promise for pain and treatment-resistant depression. However, its antidepressant effect after IV dosing diminishes with time and long-term repeated IV use has not been sufficiently studied. Ketamine infusion clinics have popped up at major cities in the US, indicating unmet needs in treating PTSD with traditional pharmaceuticals.

Infusions are expensive, ranging from \$300-\$2000 per IV infusion, depending on dose and indication for treatment. Each infusion lasts an hour or more followed by an observation period for vital signs and side effects. Psychiatric side effects are frequent as well as elevated blood pressure and nausea. Insurance does not cover the infusions, and therapy can be cost prohibitive.

Ketamine is reported to be a robust and rapid-acting antidepressant, although the effect is transient. IV ketamine in treat-



ment-resistant depression usually results in improved mood within 4 hours, reaching peak at 24 hours. The effect is diminished at 7 days, and most patients relapse within 10 days, although for a significant minority, the improvement may last 30 days or longer. The challenge with IV ketamine treatment is what to do when its anti-depressive effect wears off. Maintenance IV therapy, from twice weekly to once every 2 weeks, appears promising but is a costly option.

Even at low sub-anesthetic intravenous doses, psychiatric side effects are prominent. A majority of patients report feeling “strange, spacey, woozy or floating” or having visual distortions or numbness. Also mentioned frequently is difficulty speaking, confusion, euphoria, drowsiness, and concentration problems. Psychotic symptoms such as “going into a hole, disappearing, feeling melting, experiencing colors, and hallucinations” are described by around 10% of people. Dizziness, blurred vision, dry mouth, hypertension, nausea, increased/decreased body temperature, or feeling flushed are common non-psychiatric side effects.

Adverse effects are most pronounced near end of infusion. They are significantly reduced by 1 hour and generally resolve

by 4 hours. Accordingly, a several-hour period of observation is recommended after ketamine infusion. Patients are not recommended to drive home afterward.

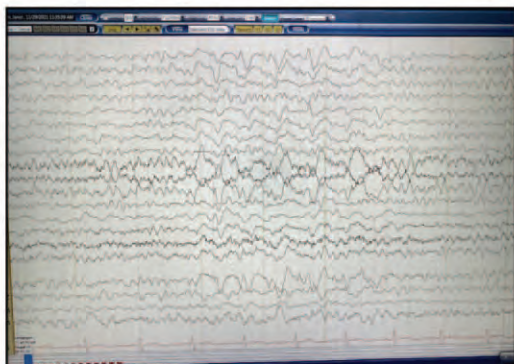
Ketamine has not been approved as an antidepressant in the US, but the Canadian Network for Mood and Anxiety Treatments recommends it as a third line treatment for depression. An enantiomer of ketamine, esketamine, has been approved as a nasal spray for treatment-resistant depression in the US and elsewhere. Intravenous ketamine has not been directly compared with intranasal esketamine, but a comparative meta-analysis of clinical trials suggested IV ketamine’s superiority. There were greater overall response and remission rates and less dropouts from side effects.

Ketamine is used as a recreational drug in powder and liquid forms for its hallucinogenic and dissociative effects. At sub-anesthetic doses, ketamine produces a dissociative state, characterized by a sense of detachment from one’s physical body and the external world, known as “depersonalization” and “derealization.” At sufficiently high doses, users may experience what is called the “K-hole,” a state of dissociation with visual and auditory hallucinations similar to the effects of LSD.

NeuroDirect™ Topical Ketamine Therapy: EEG Changes

8 patients had NeuroDirect ketamine applied during EEG recording and exhibited appreciable EEG improvement 3-5 minutes after treatment:

Example #3



Patient #61

Baseline abnormal EEG improved significantly after NeuroDirect™ Ketamine

Because of its ability to cause confusion and amnesia, ketamine has been used for date rape.

Liver and urinary toxicities can occur with regular high-dose ketamine use, such as occurs in recreational use. Ketamine is an NMDA receptor antagonist, which may account for most of its actions. Its anti-depressive effects remain an area of debate and research. Ketamine is on the World Health Organization's List of Essential Medicines and is available in generic form.⁴⁷⁻⁵⁰

NEURODIRECT™ KETAMINE AS NON-SYSTEMIC THERAPY

It is apparent ketamine can play an important role in treating intractable symptoms of PTSD. But, limiting use is expensive, inconvenience of infusions, poten-

tial systemic side effects, and impracticality of maintenance therapy.

NeuroDirect™ (also known as Direct Effects™ technology) is a novel, patented delivery of neuro-active compounds as cream applied to skin at the back of neck at the hairline (BONATH). BONATH is critical area of anatomy where access to afferent neural input to spinal cord and brain is achieved through Trigeminal and Vagal Nerve Complexes. Free nerve-endings under skin surface are activated by topically applied active drug, with neurochemical reactions occurring at specific receptors. Action potentials to central nervous system resulting from chemical reactions provide therapeutic benefit. This occurs without requirement of drug entry into bloodstream, a main source of side effects and drug interactions. The psychogenic effects encountered with intravenous and other systemic ketamine uses

are avoided. With NeuroDirect technology, benefits of psychedelic compounds may be achieved without concern for their potential systemic effects.⁵¹

Neuro-active compounds that have been successfully used with NeuroDirect technology include: triptans, dopamine agonist apomorphine, tizanidine, phentermine, 4-amino pyridine; cannabinoids, in particular, CBD, CBG, and beta-caryophyllene; as well as opioids, amantadine, tramadol, and others. In all these topical drug applications, therapeutic benefit was generally noted within 10-15 minutes of application, as nerve impulses from skin-free nerve-endings to brain travel at essentially the same rate for all individuals. Such is not so when gastrointestinal absorption and blood flow factors are involved, which even differ in an individual, depending on gastrointestinal and hemodynamic functions at the time.

NeuroDirect™ Topical Ketamine Therapy: patient #28 B.M.

Hamilton Depression Scale Before & After Treatment
(After 15 minutes)

Before Ketamine Baseline
Score 47

After Ketamine
Score 7

Desyrel® Dividose® (amitriptyline HCl)

HAMILTON DEPRESSION RATING SCALE

Before Ketamine Baseline

After Ketamine

UNIQUE NATURE OF NEURODIRECT™ TOPICAL KETAMINE THERAPY FOR PTSD

gesic, and psychomimetic effects of ketamine. Analgesia occurs through prevention of central sensitization in spinal dorsal horn neurons interfering with pain transmission to the brain. Ketamine's antidepressant mechanism of action is less certain. It is likely the NMDA receptor is not solely responsible and other receptors are involved. NMDA receptors exist on peripheral nerves and skin-free nerve-endings, allowing receptor antagonism to occur at these sites with topically applied drugs such as ketamine. This allows for ketamine's benefits in pain, depression, and anxiety relief associated with PTSD.⁴⁹⁻⁵⁰

allows potential undesirable side effects to be avoided, with therapeutic benefits achieved rapidly.

NEURODIRECT™ KETAMINE
OBSERVATIONAL CLINICAL DATA

Observational data from an out-patient Neurology and Neuropsychiatry practice in 100 patients with intractable depression, anxiety, and other symptoms commonly associated with PTSD, indicated relief of symptoms with NeuroDirect ketamine applied as a cream on skin at BON-ATH. Initial dose was 100 mg/ml; but subsequently, with a different formulation, 25 mg/ml was found equally effective. Initial and maintenance dose is now 25-50 mg/ml depending on patient need. Subjects were patients with symptoms related to PTSD for a long time, having failed nu-

TABLE 2

NeuroDirect™ Topical Ketamine Therapy:**Top Presenting Symptoms Relieved After Treatment***(Within 8-10 minutes After Application & Lasting 4-6 hrs.+)*

Anxiety = 82 patients
 Pain = 23
 Depressed mood = 22
 Cognitive processing issues = 13
 Detached /unemotional / withdrawn = 12
 Guarded/Paranoid = 6
 Reduced concentration = 5
 Agitation = 4
 Tremors = 3

Immediate response reported by patients after ketamine application

Relaxed/Calm = 58 patients
 Reduced anxiety = 35
 Reduced pain = 23
 More interactive/spontaneous = 19
 Clearer thought processes = 16
 Improved alertness/focus/concentration = 15
 Improved mood = 14
 More open/honest = 12

merous previous other treatments. Many were significantly symptomatic while on several pharmaceuticals as well as herbal products, such as CBD and cannabis.

Discernible improvement in anxiety, depression, paranoia and unrealistic fear, focusing issues, cloudy thinking, neuropathic pain, and other such symptoms were noted within 8-10 minutes of topical drug application. Benefit by patients was also noted by family members and other objective observers. In some instances, clinical improvement was documented by objective measures, such as the Hamilton Depression Scale and EEG tracings.

More than 80% of patients trying NeuroDirect topical ketamine found it effective to the extent formal prescriptions were requested for continued use at home. As with any therapeutic intervention, patient selection is key in determining clinical response. No psychogenic effects, such as hallucinations or dissociative phenomena, were experienced by any patient. To the contrary, patients indicated their thought processes were clearer, more focused; and, that they were more keenly aware of

surroundings.

Initial ketamine dose was 25-50 mg: 1-2x/day. Less "wearing off" phenomena with return of symptoms was seen with longer continued use, suggesting "de-programming" of PTSD-related neural circuits. Some patients reduced dosing after 2-3 weeks. After a period, some patients were even able to change to use on "as needed basis." In more severe chronically affected individuals, 25-50 mg every 2-3 days was generally required as maintenance therapy. Using the NeuroDirect topical ketamine, a significant number of patients were able to reduce or discontinue prior medications.

Table 1 provides a breakdown of diagnoses of the 100 treated patients. Middle-aged females with PTSD predominated; there were 61 females and 39 males. Ages ranged from 12 to 90 years. Table 2 shows top presenting symptoms relieved by ketamine therapy and immediate responses noted.

Eight patients had NeuroDirect ketamine applied during EEG recording. All exhibited EEG improvement 3-5 minutes

after treatment. Figure 1 is an example one such patient.

The Hamilton Depression Rating Scale (HAM-D) is a multiple-item questionnaire that provides indication of depression and guides in evaluating treatment response and recovery. The questionnaire is self-assessed, with occasional input of a significant other/spouse/family member as corroboration. It rates severity of depression, anxiety, and other symptoms that may be associated with PTSD. It evaluates mood, feelings of guilt, suicide ideation, insomnia, agitation, retardation, anxiety, weight loss, and other somatic symptoms.

Figures 2 and 3 show changes in the Hamilton Depression Scale in two patient examples. One is immediately after ketamine application, and the other, 2 weeks after continuous twice-daily therapy. Six patients studied before and after treatment with ketamine, exhibited reduction in HAM-D scores of 40, 22, 13, 11, and 7 points 15 minutes after ketamine application.

SUMMARY

In view of the preliminary observational data, formal controlled studies need to be undertaken and steps taken to make this revolutionary product more widely available. It is more cost-effective, convenient, and appears more effective than currently available treatments using systemic ketamine for PTSD symptoms. Additionally, there is no concern for psychogenic and other systemic effects.

The following is a testimonial from a patient who used NeuroDirect ketamine: "It was like truth serum! I became aware of thoughts and emotions I had suppressed which needed to come out. I

FIGURE 3

NeuroDirect™ Topical Ketamine Therapy: patient #72 Diane H.

Hamilton Depression Scale Before & After Treatment

(After 2 weeks)

Before Ketamine Baseline
Score: 41

(Scale Range: 0-100)

After Ketamine twice daily for 2 weeks
Score: 28

Desyrel® Dividose®
(trazodone HCl)

HAMILTON DEPRESSION RATING SCALE 41

Instructions: This checklist is to assist you in recording your evaluation of each patient with respect to degree of depressive and psychological conditions. Please fill in the appropriate rating for each item.
0 None 1 Mild 2 Moderate 3 Severe 4 Extreme

ITEM	RATING	ITEM	RATING	ITEM	RATING
1 Depressed Mood	3	11 Anxious (General)	2	21 Depressed (Anxious)	2
2 Guilt Feelings	3	12 Anxious (Specific)	3	22 Depressed (Anxious)	2
3 Suicide	1	13 Anxious (Hypochondria)	0	23 Depressed (Anxious)	2
4 Social Inhibition	3	14 Anxious (Obsessive)	0	24 Depressed (Anxious)	2
5 Irritability	4	15 Anxious (Phobic)	0	25 Depressed (Anxious)	2
6 Delirium	1	16 Anxious (Hypochondria)	0	26 Depressed (Anxious)	2
7 Work and Interest	3	17 Anxious (Hypochondria)	0	27 Depressed (Anxious)	2
8 Anorexia	4	18 Anxious (Hypochondria)	0	28 Depressed (Anxious)	2
9 Insomnia	2	19 Anxious (Hypochondria)	0	29 Depressed (Anxious)	2
10 Anxious (General)	2	20 Anxious (Hypochondria)	0	30 Depressed (Anxious)	2

17-ITEM SUB-TOTAL: 34

25-ITEM TOTAL: 41

Desyrel® Dividose®
(trazodone HCl)

HAMILTON DEPRESSION RATING SCALE 28

Instructions: This checklist is to assist you in recording your evaluation of each patient with respect to degree of depressive and psychological conditions. Please fill in the appropriate rating for each item.
0 None 1 Mild 2 Moderate 3 Severe 4 Extreme

ITEM	RATING	ITEM	RATING	ITEM	RATING
1 Depressed Mood	2	11 Anxious (General)	1	21 Depressed (Anxious)	0
2 Guilt Feelings	0	12 Anxious (Specific)	2	22 Depressed (Anxious)	0
3 Suicide	0	13 Anxious (Hypochondria)	0	23 Depressed (Anxious)	0
4 Social Inhibition	1	14 Anxious (Obsessive)	0	24 Depressed (Anxious)	0
5 Irritability	3	15 Anxious (Phobic)	0	25 Depressed (Anxious)	0
6 Delirium	0	16 Anxious (Hypochondria)	0	26 Depressed (Anxious)	0
7 Work and Interest	1	17 Anxious (Hypochondria)	0	27 Depressed (Anxious)	0
8 Anorexia	0	18 Anxious (Hypochondria)	0	28 Depressed (Anxious)	0
9 Insomnia	0	19 Anxious (Hypochondria)	0	29 Depressed (Anxious)	0
10 Anxious (General)	1	20 Anxious (Hypochondria)	0	30 Depressed (Anxious)	0

17-ITEM SUB-TOTAL: 10

25-ITEM TOTAL: 28

found myself crying uncontrollably as I released them. It allowed me to move forward as I had been stuck in a rut. I began to feel so much better as I faced how selfishly and un-lovishly I had treated my ill mother before she suddenly passed away." Another stated "The usual triggers no longer affected me to go into a panic state..." ♦

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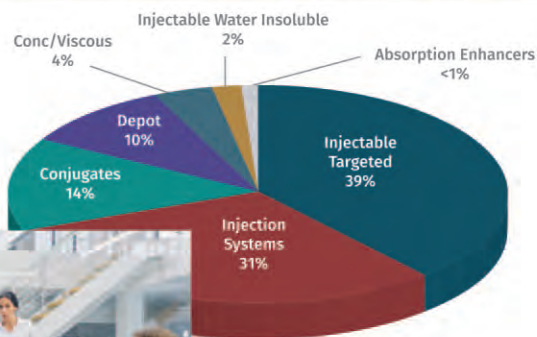
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Excipient vs Strength

	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

Screen Potential Partnering and Investment Opportunities

Select Companies

Amgen Inc. x
Biogen, Inc. x

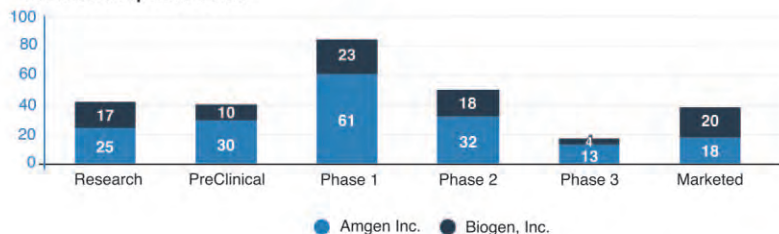
Attribute Type

- ☐ Gross Profit
- ☐ Net Income
- ☐ Number of Employees
- ☐ Operating Income
- ☐ Research and Development Expenses
- ☐ Sales, General and Admin. Expenses
- ☐ Total Assets
- ☐ Total Current Assets
- ☐ Total Current Liabilities
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BIOGRAPHIES



Dr. Ronald Aung-Din practices General Neurology & Neuro-Psychiatry in Sarasota, FL. He is board-certified by the American Board of Psychiatry & Neurology and member, American Academy of Neurology. After earning his Bachelor's and Master's degrees in Engineering at Bucknell and Cornell Universities, he worked for a period as a supervising engineer. He then attended Columbia University in New York City for Premedical studies, followed by Medical School at University of Texas Southwestern Medical School, Dallas, TX. Residencies in

Neurology and Neurosurgery were at University of Florida. Other studies included a Medical Student Fellowship in Cardiology at Radcliffe Infirmary, Oxford and Clinical Neurology Fellowship at National Hospital for Nervous Disease, Queen Square, London, UK. He has participated in over 60 pharmaceutical industry-sponsored clinical trials, functioning as Principal Investigator in drug research studies in MS, epilepsy, pain, Parkinson's disease, and other neurological diseases. He is also active in treating varied neurological and psychiatric conditions using delivery of CNS-active drugs with NeuroDirect™ technology, developed by him for which 13 US and foreign patents have been granted; with others pending. Publications using this novel therapy in migraine, Parkinson's disease, autism spectrum disorder, and diabetic neuropathy; in addition to articles on the use of cannabidiol, CBD, and the non-cannabis cannabinoid receptor agonist, caryophyllene, have appeared in *Drug Development and Delivery*. AfGin Pharma, LLC was founded by Dr. Aung-Din in 2009 to advance his unique technology and its goal of "Enhanced Neuro-Therapeutics through Direct Effects Topical Technology."



Dr. Chantelle G. Martin was born in Zimbabwe, Africa, and attended Medical School at the University of the Free State, Bloemfontein, South Africa, earning her Bachelor of Medicine and Bachelor of Surgery degree in 2016. She later completed 2 years of internship training at Grey's Hospital, Pietermaritzburg, South Africa; rotating through Surgery, Pediatrics, OB-GYN, Neurology, Internal Medicine, Orthopedics, Anesthesiology, Family Medicine and Psychiatry, where she managed a wide range of medical and surgical conditions. Later, she also did a year of rural community service as a medical officer in Pietermaritzburg. She currently lives in Sarasota, FL, awaiting a residency position. In the interim she is not only gaining valuable clinical experience but also participating in groundbreaking research with the General Neurology and Neuropsychiatry clinical research practice of Sarasota neurologist Dr. Ronald Aung-Din and his AfGin Pharma, LLC research and development bio-pharmaceutical company, founded in 2009. Her recent work with the Direct Neuro Topical use of ketamine for the treatment of PTSD and intractable depression is an example of the value she provides in clinical research, advancing novel non-systemic technologies for difficult neurological and psychiatric disorders. Her passion for finding treatments for diseases of the nervous system using neuro-psychotropic drugs is evident and an added bonus to her contribution to medical pharmacotherapeutics.

FORMULATION FORUM

Changing the Landscape of Nanoparticles for Long-Acting Injectable Drugs

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



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INTRODUCTION

The continued research efforts in areas regarded as long-acting injectables, long-acting parenterals, long-acting depots, depot formulations, sustained-release parenterals, and controlled-release parenterals, have led to an exponential growth in the past two decades (Figure 1).¹ Nanoparticles (NPs) play a crucial role in extended-release of long-acting injectable (LAI) formulations. Recently, there has been continued interest in parenteral NPs with sustained-release characteristics as more drugs discovered are poorly soluble and less bioavailable.² These challenges have led to enormous opportunities and launch of many drug products to market.

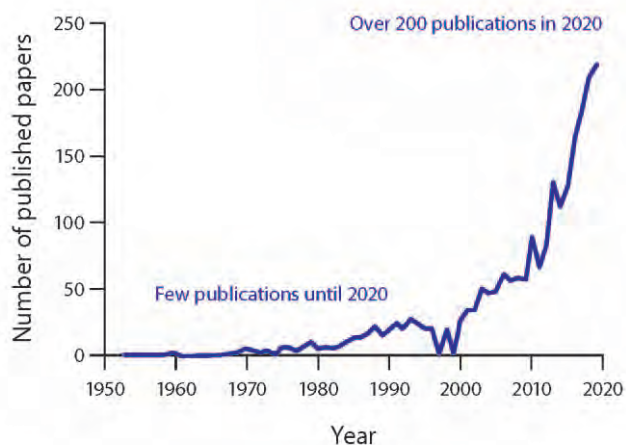
The significant growth stems from innovative approaches for developing LAI products that require less-frequent administration for longer and controlled release, and for safety and efficacy of drugs. Less

frequent and controlled release equally make LAI more attractive from patient compliance perspectives as one dose can lead to extended release over several weeks and possibly months.³ As nanoparticle technologies continue to yield better and smarter formulations with longer release profiles, the industry is open to adapt more innovative approaches to expedite the process for bringing new drugs to market. The appropriate regulatory guidance on addressing complex molecules, novel excipients, or technologies, for example, could have an impediment in the approval of new drug products.⁴ Other challenges, such as lack of guidance on test method, validation, manufacturing, particle size reduction, high pressure homogenization, sonication, extrusion, milling, solvent impurities, stabilization, and lyophilization may cause further delays.

Nanoparticles are derived from polymers, lipids, and surfactants/co-surfactants, and oils with unique identities based on the fatty acid characteristics and compositions, polar and non-polar headgroups, and hydrophilic and hydrophobic nature of polymeric chains. The particle size and dispersibility in aqueous solutions depends upon hydrophilic and lipophilic balance (HLB), molecular weight, and polydispersity. The encapsulation and drug loading characteristics are dependent upon drug molecules and interstitial spaces within the polymeric or lipid assemblies. Thus, encapsulation, loading, stability, and efficient delivery might be relevant factors in selecting preferably one technology over the others.

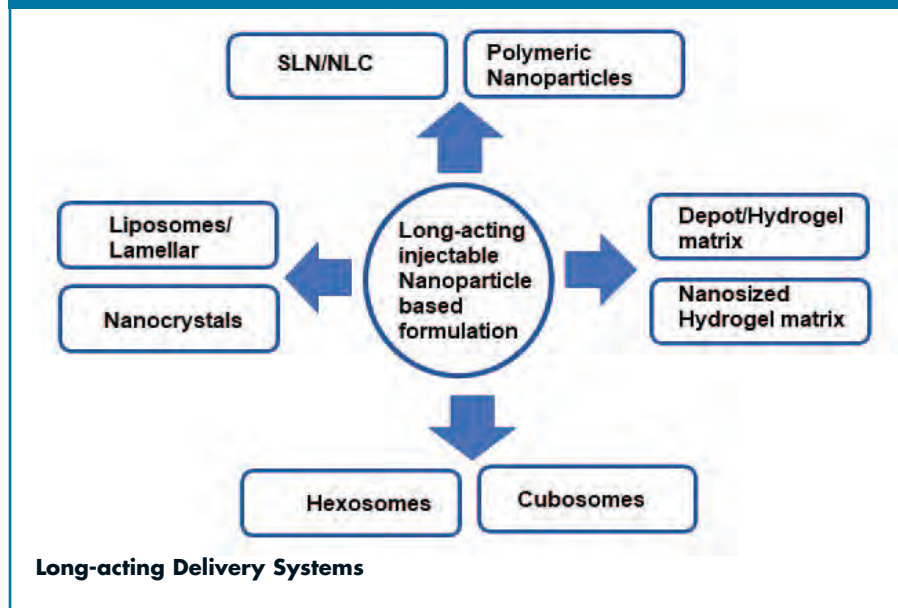
LAIs enable slow and controlled release, slower clearance rate, and resistance to enzymes with longer stability and extended half-life.⁵ Figure

FIGURE 1



Recent trends in long-acting injectables based on literature citations

FIGURE 2



2 illustrates the long-acting formulations that are categorized as SLN/NLC, polymeric nanoparticles, nanocrystals/nanosuspensions, hydrogels, depots, lamellar assemblies, such as liposomes, cubosomes, and hexosomes, and also into long-acting microneedles and/or implants. Finding the appropriate NP technology for a potential drug candidate depends on multiple factors, most notably the robust design, excipient selection and compatibility, efficient delivery, and long-term stability.

As the interest in LAIs continues to grow, the industry is adapting the innovative technologies and different strategies for launching new drug products. The key strategies are to help increase half-life and retard the release of drug in the systemic circulations to maximize the efficacy. Those strategies may include chemical modifications, PEG-ylation, lipidation, nucleic acid modification from *in vivo* clearance perspectives, microencapsulation, multi-vascular liposomes, oil-based assemblies, nanocrystals, hydrogels, microneedles, and implants as delivery systems.⁶

This following will focus on lipid-based and nanocrystal suspension nanoparticles

designed for efficient and sustained delivery of drugs.

LONG-ACTING INJECTABLE LIPID-BASED FORMULATIONS

Throughout the years, many drugs have been launched, but only a few are listed in Table 1. Of them, some are designed in liposomes, others in surfactants, polymeric nanoparticles, and nanocrystals for different modalities.

Lipid-based LAIs are oils, aqueous suspensions, and olegels. There are several oil-based LAIs approved in the market, eg, with

castor oil (Faslodex[®]), cotton seed oil (Depo-Testosterone[®]), sesame oil (Haldo[®]), and cotton seed oil (Clopixol[®]), and all are administered intramuscularly (IM). LAI activities of these drugs stem from lipophilic fatty acid derived prodrugs that allow the cleavage of the parent molecule by hydrolysis of ester linkages. While the longer fatty acid slows down the release of drug due to higher partition barrier from oil phase to aqueous phase in an oil-based or suspension-based LAIs, it also runs risk for reducing potency of parent molecules.⁷ Lipophilicity and higher log P tend to slower release following IM injection, allowing the API uptake predominantly by lymphatic systems.⁸ In cases in which API is hydrophilic, for example, olanzapine, molecular modification with fatty acid can further reduce the solubility to offset the rapid release, making it ideal for sustained release and uptake by lymphatic systems.⁹

Other factors, such as viscosity of injectable oils, may have a significant impact on release of drugs. Sesame oil and organogels with higher viscosity and having an excellent tolerability by IM, can lead to slower release and partitioning by diffusion mechanism from oil/gel into body fluid. Suspensions in oil of drug crystals is an alternative oil-based LAI. It is different from the suspensions in aqueous for injection. Oil-based suspensions have limited scope because of difficulty to inject and pain at the injection site;

TABLE 1

Product	Nanocarrier	API	Route	Indication
Abelcet [®] /AmBiosome [®] /Amphtec [®]	Ribbon-like structures/Liposome/disc like structure	Amphotericin B	IV	Fungal infection
Abraxane [®]	Albumin-paclitaxel conjugate	Paclitaxel	IV	Oncology
DaunoXome [®]	Liposome	Daunorubicin citrate	IV	Oncology
DepoCyt [®]	Liposome	Cytarabine	Intrathecal	Oncology
Diprivan [®]	Nanoemulsion	Propofol	IV	Anesthesia
Eligard [®]	Polymeric nanoparticle	Leuprolide acetate	SC	Oncology
Fungizone [®]	Micelle	Amphotericin B	IV	Fungal infection
Myocet [®]	Liposome	Doxorubicin	IV	Oncology
Opaxio [®]	Polymeric nanoparticle	Paclitaxel	IV	Oncology
Visudyne [®]	Liposome	Verteporfin	IV	Osteoarthritis

Table 1 shows the list of FDA drugs approved in lipid and polymeric based NPs.¹¹

TABLE 2

Product	API	Route	Indication
Agofollin Depot®	Estradiol benzoate	SC	Hypoestrogenism
Aristada®	Aripiprazole lauroxil	IM	Schizophrenia
Betason® L-A	Penicillin G benzathine	IM	Syphilis, prophylaxis
Depo- Medrol®	Methyl prednisolone acetate	Intra-articular	Epicondylitis
Invega Sustenna®	Paliperidone palmitate	IM	Schizophrenia
Invega Trinza®	Paliperidone palmitate	IM	Schizophrenia
Kenalog®	Triamcinolone acetonide	IM, intravitreal	Arthritis, infection
Zyprexa®	Olanzapine pamoate	IM	Schizophrenia
Relprevv®	Olanzapine pamoate	IM	Schizophrenia

Marketed drugs in nanosuspension LAIs.¹³

therefore, aqueous-based LAI suspensions are preferred as alternative options than oil-based suspensions. Lipid-based liquid crystal forming systems are another alternative to LAI formulations. The liquid crystalline ability of lipids can provide a controlled-release mechanism by entrapping the drugs into the inner core of the fatty acid lipids. Hence, the sustained release is a result of slower diffusion of drug through the mesophase membrane. There are three mesophases (lamellar, hexagonal, and cubic with hexagonal) that are widely studied.¹⁰

In addition, a number of polymeric and lipid-polymer hybrid nanoparticle LAIs have been tested in the preclinical substance use disorders (SUDs) by subcutaneous and intramuscular routes of administration for nicotine and cocaine vaccines.¹²

NANOCRYSTAL SUSPENSIONS

Throughout the past 2 decades, there has been a continued interest in nanomilling for achieving the desired particle size for controlled release of drugs. The top-down and bottom-up approaches have been generally used to obtain the desired particles to achieve longer release profiles from injections. These approaches suffer with some challenges if the drug is poorly soluble, thus, making the risk factors higher if it requires higher doses. Therefore, the efforts have been focused on liquid long-acting nanosuspensions with solubilizers and anti-flocculating processing aids for higher drug loading, making them more patient compliant and improving the safety profile long-term.

Several drugs have been marketed in nanocrystal suspensions, including the antipsychotic drug Invega Sustenna®

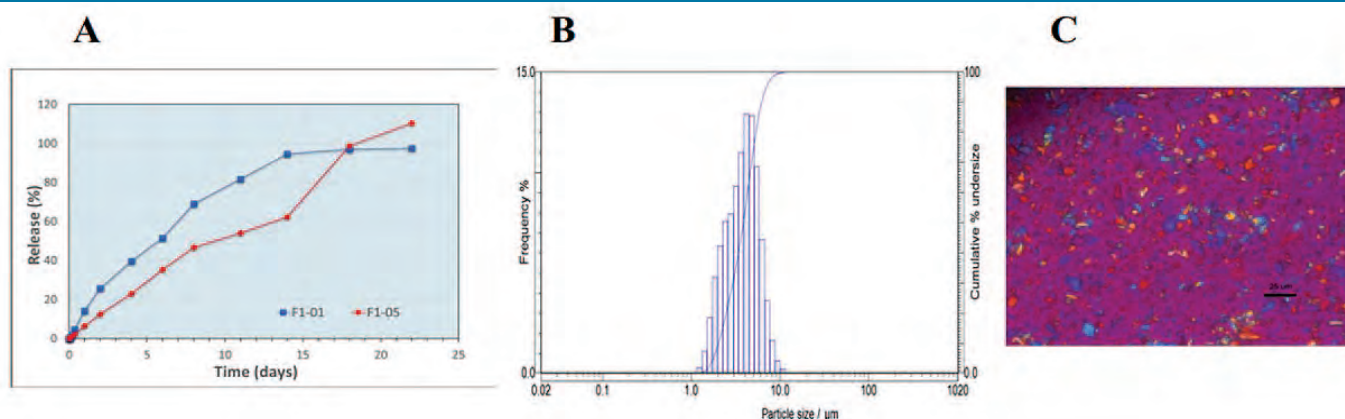
(paliperidone palmitate), and its prodrug Invega Trinza® (paliperidone palmitate) among others as shown in Table 2.

In preparation, it requires wet milling or high-pressure homogenization, and the resulting LAI nanosuspensions can be lyophilized for improving the longer shelf-life. Figure 3 shows the drug release from nanosuspensions having the particle size distribution range of 100-1000 nm as observed by light microscopy. The extended release of drug lasts for several days from the nanosized crystal suspensions.

SUMMARY

As we continue to innovate new molecules, the industry is weighing all options and assessing nanoparticle technologies for the development of potential drug candidates. Significant progress, however, has been made in LAIs to meet the clinical needs but is far from over as more challenging molecules continue to be discovered to address the unmet medical needs for treatment of life-threatening ailments and for life cycle management. Dose variability and poor patient compliance pose safety risks, which warrant further assessments of nanoparticle technologies to formulate the new LAI candidates for oncology, antivirals, CNS,

FIGURE 3



Nanosuspensions showing extended-release profiles (A) from a controlled particle size distribution, (B) recorded by laser diffraction, and as observed by light microscopy (C).

and metabolic diseases among other modalities. Thus, there is a continued paradigm shift in the design and development of nanoparticles for injectable drugs. All these challenges point to the fact that LAIs are very promising innovations with great potential to market. Ascendia's capabilities in solubilization-enabling technologies are relevant in helping the industry working with small and large molecules and biologics and gene delivery. Our expertise in lipid-based LipidSol®, NanoSol®, and EmulSol® formulations and cGMP manufacturing and lyophilization capabilities of injectable drugs, can help provide the tailor-made solutions leading to expedited development of lead candidates from early stage to late stage in the clinics and commercialization of drug products. ♦

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MARKET TRENDS

Emerging Trends in Injectable Drug Formulation & Delivery

By: Martin Gonzalez, PhD

INTRODUCTION

An extremely broad range of increasingly advanced therapeutics are administered via parenteral administration. The stars of the show recently are the billions of messenger RNA (mRNA) inoculations that continue to be delivered globally. Now a blockbuster technology, mRNA-based pharmaceuticals are poised to take off in the very near future and could lead to a huge growth in parenterally administered drug products.

STERILE INJECTABLES INNOVATION DRIVING GROWTH

Markets for all sterile injectable (SI) drugs and their delivery devices are growing at an exponential rate. Although the number of SI therapeutics consumed globally is dwarfed by solid oral forms, more and more pharmaceuticals are being delivered to patients parenterally.

The uptake of biopharmaceuticals by global healthcare to treat conditions like arthritis and diabetes is driving significant global growth. According to Precedence Research, the global biopharmaceutical market is predicted to reach \$856.1 billion by 2030 and expand at a compound annual growth rate (CAGR) of 12.5% from 2021 to 2030.¹

MRNA LEADS THE WAY POST PANDEMIC

Prior to the pandemic, mRNA-based drug products were primarily focused on treating oncology indications rather than infectious diseases. In the wake of COVID-19, technical and scientific advancements have allowed researchers to expand the

use of mRNA to new therapeutic areas. For example, lipid carriers for mRNA were also further developed, increasing the potential of mRNA technology by prolonging antigen expression *in vivo*.² What's notable is the response to the pandemic advanced the science, which proved instrumental to the success of COVID-19 vaccines and highlighting the enormous potential of mRNA technology.

With mRNA-based drugs experiencing a surge in development and demand, companies supporting the commercial manufacturing of those products had to adapt quickly to overcome the challenges involved. Virtually overnight, mRNA became the premier technology for much of global pharma. The impact has been significant, and investment in mRNA's therapeutic potential has been tremendous. By the end of 2019, for example, the combined market capitalization of the five publicly listed companies focusing on mRNA platforms was \$15 billion.³ By the third quarter of 2021, market capitalization of the sector was more than \$300 billion.⁴

INTRODUCING TRANSFORMATIONAL CELL & GENE THERAPIES

Now grouped by regulators as Advanced Therapy Medicinal Products (ATMPs), gene and cell therapies (CGTs) are also transforming pharmaceutical-based healthcare. They continue to demonstrate significant therapeutic results for patients and demonstrate the potential to cure disease by addressing the root cause of the condition. The science behind these therapies as well as the means to deliver them is advancing at a lightning pace. Valued at \$12.3 billion in 2021, the ATMP market is predicted to reach a market value of \$59.9 billion by 2031.⁵

Recent breakthroughs in the CGT space have spurred the



Analysts working in HPLC systems (in our Pfizer CentreOne Tech Services cGMP lab).

flow of investment to the sector. This growing cash infusion is expected to accelerate the pace of development further, especially as life-science developers work toward increasing patient access. The American Society of Gene and Cell Therapy noted in its Gene, Cell, and RNA Therapy Landscape Quarterly Data Report (Q4 2021) that - of the 3,483 CGTs are currently in development globally - 32 are in Phase 3, an increase of 10% from the previous quarter.⁶

STERILE INJECTABLES MOVE INTO THE MAINSTREAM

A third or more of all pharmaceuticals are manufactured by external partners. This means the pressure is on the industry's CDMOs to find more cost-efficient ways to speed up production and provide a shorter path to market. For many, this will prove extremely challenging – and likely to prompt renewed facility investment. Although new ways of delivering sterile formulations are being introduced, subcutaneous and IV delivery via needle

will – more than likely – remain the dominant administration route for SI drugs.

INJECTABLES WITH LESS STING

Contemporary drug design and much of its emphasis has shifted from just preserving basic quality attributes, such as safety, efficacy, and potency in a simple container. Today's SI drugs carry a more complex profile and offer a new approach to extending the value of the therapy to patients, while providing additional benefits to the patient, including better dose compliance.

The patient's experience has influenced the development of new and creative ways to deliver sterile formulations, including patches that subcutaneously penetrate the skin, degradable implants, and other innovative methods to deliver sterile formulations. According to Fortune Business Insights data, the global injectable drug delivery market was valued at \$483.4 billion in 2019 and is projected to reach \$1,251.2 billion in size by 2027

rising at a compound annual growth rate (CAGR) of 12.9%.⁷ The SI market is a rapidly evolving industry. A clear example of this is the explosive creation of pharma companies devoted to developing therapies and treatments for COVID-19.

SELF-ADMINISTERED PARENTERALS TAKE CENTER STAGE

For millions of patients who dose themselves frequently, there is a growing preference for smarter, friendlier ways to self-administer injections. This patient focus has led to widespread medical device innovation over the past 2 decades, including pre-filled syringes, injector pens, and automated injection and infusion devices.

Syringe needle technology has also been exposed to a long and continuous development cycle that continues to introduce patient-centered innovation. They're now engineered to support less painful subcutaneous and IV delivery, as well as



HPLC Bank for Sample Testing

manage the flow of drug substance from device to patient. Small bore needles, “low pain” (27 G to 31 G gauge), are engineered and fabricated to reduce pain and discomfort at the injection site. However, a small bore needle might increase the risk of clogging, making the injection more difficult and less predictable. Challenges also exist for high-concentration products, such as product shear, or higher infusion pressures that these devices need to be able to handle. There’s already a multitude of pump designs that can cope with these issues, but there isn’t a one-size-fits-all solution yet.

Prefilled syringes, unit-dose autoinjectors, and similar delivery methods have dominated the market for years due to their simplicity and ease of use. Among those technologies, analysts note prefilled syringes represent the fastest-growing segment. In 2021, the global prefilled syringes market was valued at \$5.8 billion. The overall market exhibited strong growth and is expected to grow to \$11.9 billion by 2028 at a (CAGR) of 10.7%.⁸

Although connected autoinjectors, such as infusion pumps for delivering insulin, have only been on the market for a shorter time, innovators are increasingly taking advantage of these technologies

because they are proving to increase patient-friendliness and promote better therapeutic outcomes.

APIS TO THE RESCUE

In the near-term, developing formulations and matching them to existing and new devices is going to keep the industry extremely busy. Advanced active pharmaceutical ingredient (API) formulation techniques are being developed to protect these drug products from degradation and the impact of processing and manufacturing. Formulators are exploring ways to avoid enzymatic damage upon release, providing a more precise targeted delivery of the API while controlling attributes related to their pharmacokinetic profile (biocompatibility and bioavailability).

Reducing dosing frequency and the overall number of injections is another patient-facing challenge being addressed by the industry in formulation. Although long-acting-injectables (LAIs) and multi-API combined formulation concepts offer workable solutions to reduce dose frequency, they can and will introduce complexity into formulation and device development prevalent currently.

Many drug substances, particularly biologics, can be highly viscous in final formulation due to their concentration and dosing requirements, mandating it be kept to minimum volume. Because subcutaneous injections are limited to small volumes, usually 1 mL to 3 mL, even when wearable delivery devices are employed, only slightly larger volumes can be delivered over time but even then, there are limits to what patients can tolerate.

Further, converting a formerly IV drug formulation to one that can be administered subcutaneously requires an increase in concentration and likely some reformulation to improve flow and injection pressures to reduce pain/stinging/edema at the injection site.⁹

This can make dispensing and administration fraught with difficulty as patients generally prefer subcutaneous injections of parenteral drugs, as opposed to intravenously and in a clinical setting. This is especially true for therapeutics that require frequent dosing and a major driver of the development of higher concentration biologic formulations as well as increasingly sophisticated ways to deliver doses accurately and with less pain. The adoption of subcutaneous self-administration also removes the need for patients to spend hours in a clinical setting to receive the drug. It also makes treatment less expensive to both payer and patient.

NEW ENABLING TECHNOLOGIES SUPPORTING INNOVATION & DEVELOPMENT

Lipid Nanoparticles (LPNs) are an emerging enabling platform technology for the delivery of active biopharmaceutically relevant molecules (biologics or small

molecules), including mRNA. With the advent of increased mRNA, it is opening up a lot of new possibilities for companies to innovate their mRNA technology IP and differentiate their products in the marketplace.

Spray Freeze-Drying (SFD) technology is becoming a useful tool for manufacturing lyophilized sterile injectable products. It has the potential to increase throughput and increase options for manufacturing, fill, and fill finish as well as other opportunities to introduce efficiencies and accelerate timelines.

Analytics are being introduced that will have the same positive impact on development. For example, technologies that facilitate fast formulation screenings. These “lab-in-a-chip” systems conceptually are a marriage between a plate reader handler instrument to one or several optical-type detectors in one box. The device allows the multi sampler holder (usually a 48-well plate) outputs to be read very quickly, repetitively, and with a minimal quantity of study material.

COMPLETING THE PUZZLE

Increasingly, the CDMO industry is tasked with putting all the pieces of this puzzle together – from formulation to finished drug product – and preparing products for commercial markets and patients. In their contemporary form, SI delivery devices offer a number of challenges to develop successfully. High-potency biologics come with higher viscosities, problematic shelf-lives, logistics issues, and other impediments to commercial development. As the pandemic gained momentum, the industry began to realize that “time to market” can be shrunk tremendously with the

right technology and technical tools.

As for the technical tools mentioned previously, similar to all the manufacturing equipment and analytical techniques associated with advancing drug projects, it is worth mentioning that if pandemic taught us anything, it is that investing in technology can have a huge impact on timelines.

A clear example is the ongoing integration of information technologies and applying them effectively to project management. For example, subject matter expert groups from both CDMOs and their customers introduced the capability to conduct virtual face-to-face meetings in real-time, cutting down the occurrence of “will get back to you” lag while providing answers or solving issues on the spot. In that one significant way, overall project timelines are no longer the same as they were 5-10 years ago.

When evaluating a drug substance’s presentation and appropriateness for a delivery device, the first couple of “default options” (vial, prefilled syringe) may not prove to be the best path. Regardless of this, the chemical makeup of the drug product is prompting developers and CDMOs to pursue a deeper, more meaningful analysis – not only of the drug’s formulation properties, but also the device’s technical limitations, as well as its intended function and user experience.

Depending on the enterprise, the IP owner may understand what pieces of the puzzle need to come together, but not exactly how they should fit to create the big picture of the product as early in development as possible. Experience, technical capabilities, and expertise are required to commercialize and manufacture these sophisticated products successfully. That is why pharma’s small and large molecule developers are increasingly turning to con-

tract partners for help delivering their innovations to patients. ♦

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BIOGRAPHY



Dr. Martin Gonzalez is a Senior Manager at Pfizer CentreOne Technical Services. In that role, he leads the formulation and process development team. He earned his PhD in Biophysical Chemistry, and has more than 25 years of experience in formulation development and manufacturing processes for biologics and synthetic drug products. Having previously worked as a scientist at the US NIH’s National Heart, Lung, and Blood Institute, he has extensive expertise in plasma-derived proteins, polypeptides, enzymes, vaccines, and recombinant proteins and antibodies. This expertise has made him a subject matter expert in protein formulation, product development, and lyophilization, manufacturing troubleshooting, delivery devices, and final container selection.

SUSTAINABILITY

Is the Pharmaceutical Industry Preparing Effectively for a Greener Future?

By: Michael Earl

INTRODUCTION

To achieve the goals set out in 2021's COP 26 summit – and recently reiterated during COP 27 – governments around the globe have set targets to achieve net zero carbon emissions and create a greener future by 2050. To support this endeavor, energy-intensive sectors, including the pharmaceutical industry, are under pressure to change practices and set their own ambitious targets to futureproof operations. At Owen Mumford, we reviewed 25 of the biggest pharma companies reporting environmental, social, and governance (ESG) scores to see how the industry is performing. As a key delivery device partner for pharma companies, it is also critical we improve our own processes. The following highlights progress made to date to become more sustainable - including examples from our own journey – and emphasizes areas where development has been lacking so far.



internal resources or expertise are given the opportunity to participate in the market, and to learn more about renewable energy adoption and contracting.

ENERGY REDUCTION

Policies to reduce energy usage throughout the pharmaceutical industry are well established with a combination of renewable energy sources, self-generation of power, and increasing efficiency of manufacturing processes helping to reduce consumption.¹ In one example, leading pharmaceutical companies have joined Energize, a program aiming to accelerate the adoption of renewable energy, by examining how companies can overcome typical market barriers to renewable energy procurement.² Through the program, suppliers who may not otherwise have the

Meanwhile, manufacturing initiatives often focus on reducing energy usage throughout the production line or in industrial buildings.³ This is part of our strategy at Owen Mumford. Our UK sites are now powered by 99%+ renewable energy sources, and we generate energy ourselves from on-site solar panels. UK and French sites are both supplied by green energy tariffs, and we aim for all our electricity to come from renewable sources by 2030.⁴ Our new state-of-the-art production facility in Witney is designed to achieve BREEAM certification – the world's leading sustainability assessments for buildings – and will ensure effective deployment of energy, heating, and cooling using the latest technology and materials.

AIR EMISSIONS

Air emissions have received the most attention from pharmaceutical companies in terms of target setting. Almost 70% of companies in our review have defined targets around air emissions, to reduce both carbon emissions and various gaseous pollutants, including acid gases, dust and aerosols, pharmaceutical “actives,” and other volatile organic compounds. Targets are varied, with some setting overarching goals for emissions or carbon neutrality, while others combine these with separate targets to reduce direct and indirect carbon emissions. In line with the Paris Agreement, companies are targeting carbon neutrality by no later than 2050, with the most ambitious hoping to achieve this by 2030. Through the Science Based Targets Initiative, Owen Mumford has also set its own target of reducing emissions by 50% by 2030, with a further goal of net zero by 2045.

WASTE EMISSIONS

While all companies in our review had goals to reduce their waste, only a quarter had set targets to reduce waste emissions by at least 25%. Variance is high in this category, with the most ambitious companies targeting zero waste by the end of 2025 and others yet to set firm targets. Some approach waste reduction by attempting to avoid landfill waste, while others are determined to pursue a zero-waste strategy. Future efforts to reduce waste will rely on the ability to re-use and recycle products that have typically been difficult to dispose of or designing products using more environmentally friendly materials. In the UK, up to 23 million medical pens

are sent to incinerators or landfill every year, prompting one pharmaceutical company to launch a recycling initiative. In November 2022, the company shared that up to 700,000 pre-filled plastic injection pen devices would be recycled by the end of the year. This initiative is part of the company’s Circular for Zero strategy, which commits to net zero emissions across its entire value chain by 2045 – in line with NHS England’s ambition to become the world’s first net zero national health service by 2045.⁵

We continue to operate with zero waste to landfill at Owen Mumford. We recently introduced a new baling method that has resulted in a 90% reduction in transport and improved our opportunities for recycling. Our capabilities for sorting production waste has expanded so it can be handled through the most appropriate channels for recycling. All our sites have recycling policies for waste cardboard and cartons, and we reuse materials such as pallets whenever possible. Following the COVID-19 pandemic, we have moved our finance and HR departments online, so they are able to operate completely paper-free.

WATER CONSUMPTION

Pharmaceutical companies have typically been a major consumer of water. A variety of factors contribute to this consumption, including using water as an excipient during synthesis or as a cleaning agent for rinsing vessels.⁶ Businesses are not only looking to reduce consumption but also to clean and reprocess wastewater to reduce their environmental impact. One major company is attempting to achieve water neutrality by 2025 – mean-

ing consumption of fresh water will be balanced with recycling of wastewater. Water neutrality can be achieved through a multi-pronged approach: reducing existing fresh water consumption by incorporating reduce, reuse, and recycle principles; harvesting rainwater to offset outside fresh water use; and investing in watershed projects for sustainable water management.⁷ While water neutrality is a long way off for most, around half the companies in our review have set hard targets to reduce water consumption with most aiming to make real inroads by 2030.

POLLUTION

Pollution is one area in which sustainability progress is lacking thus far. A recent study measuring the concentration of 61 active pharmaceutical ingredients (APIs) at more than 1,000 sites in 104 countries found that only two of the rivers were not polluted.⁸ Pharmaceuticals in the environment can drive resistance of drugs and worsen Antimicrobial Resistance (AMR). Just one of the companies in our review has set targets around AMR – an area that needs swift action to prevent risks to the environment and wildlife. The longer the industry delays in taking firm action, the more difficult this issue will be to deal with, as microbes gain increasing resistance to medicine and become harder to treat. One organization working to address this is the AMR Industry Alliance, a coalition of more than 100 biotech, diagnostics, generics, and research-based pharmaceutical companies and associations joining forces to tackle AMR. Among the goals of the alliance are: investment in R&D to meet public health needs with new diag-



nostics and treatments; reducing the use of products that will increase AMR; improving access to high-quality antibiotics; and reducing environmental impact of manufacturing.⁹

PACKAGING

Packaging is also among those areas where companies are yet to make substantial progress. Although 76% of companies had policies on packaging, only 13% had set concrete targets. Delays could be due to the challenge of selecting appropriate sustainable packaging that can provide quality and rigorous hygiene standards.¹⁰ Those with targets in place have ambitious goals, with one company aiming to use 95% paper packaging in 2022, and another looking to have 100% sustainable packaging by 2025. There may be associated cost-savings, with eco-friendly packaging often leading to lower shipping costs in light of the reduced weight of packing material.¹¹

At Owen Mumford, we concluded a packaging audit in 2020 to help set goals for the future. We evaluated five packaging categories across our supply chain, focusing on carbon footprint, overall recyclability, plastics footprint, and plastics recyclability. Following this evaluation, we are looking to

use sustainable packaging materials across all our regions, eliminate double packaging, and reduce packaging waste in production through new technologies.

SUMMARY

The pharmaceutical industry is taking impressive and much-needed steps toward a cleaner future, with many valuable initiatives in place. However, there is still much work to be done before the industry as a whole can be viewed as sustainable. The variance between the sustainability performance of different firms must be eliminated to create a truly sustainable industry. Further innovations are needed, especially with regard to packaging and pollution of which current measures are lacking. ♦

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Michael Earl joined Owen Mumford as Director of Pharmaceutical Services in November 2020. He was previously the Commercial VP at Bepak, leading the commercial team there to drive growth in their substantial medical devices business. Prior to that, he worked for a number of pharma, biotech, and device companies. In a career spanning more than 35 years, he has been responsible for all aspects and stages of drug and device development and commercialisation. He has also completed a substantial number of commercial, licensing, and M&A transactions.

AUTOMATED SOLUTIONS

Automation & Shared Knowledge Pave the Way Into the Future

By: Luca Valeggia, MSc

INTRODUCTION

Automation is a vital component to fuel the labs of tomorrow and to ensure drug development continues at the rapid pace seen in response to the COVID-19 pandemic. By no means is automation a novel concept for most research labs, but its swift advancement and expansion into new fields – such as synthetic biology – have shown us that we are only witnessing the start of what is possible. Together with open access data, which allows scientists around the globe to benefit from each other's findings, it paints a bright picture of a future that is full of exciting new possibilities.

Laboratories all over the world have been shaken by the COVID-19 pandemic. This global event forced them to step up to the challenge, finding ways to handle unprecedented sample volumes quickly and efficiently for both research and diagnostics. This put automation in the spotlight, not only as a convenient tool, but a necessity, as obtaining accurate results with such speed would not have been possible if every sample was handled manually.

Alongside the need for rapid diagnostic testing, it was crucial to develop a vaccine as fast as possible, to curb rampaging infection rates, and help the world recover both medically and economically. Laboratories came together, sharing their discoveries through open access (OA) data portals to ensure breakthroughs would not only benefit one organization or country, but the entire world. This shines light on another important point – how much more we can accomplish by sharing our knowledge, instead of guarding it.

Synthetic biology has also played a major role in winning

ground against the pandemic, allowing the creation of a candidate vaccine a mere 66 days after the viral genome was released.¹ This vaccine was created using synthetic genes, an approach that is not only useful for developing vaccines, but might also be helpful in combatting cancer, making it a powerful tool for drug discovery.

SYNTHETIC IS THE NEW NATURAL

Synthetic biology is based on metabolic engineering, but takes this concept a step further to encompass non-metabolic applications, with the aim of creating new biological building blocks and systems, or improving on those found in nature. In contrast to metabolic engineering, this discipline uses a systematic approach based on generalizable methods, making synthesis and sequencing of DNA more accessible and less costly.

One of the principles of synthetic biology is the “design-build-test-learn” (DBTL) cycle, which helps achieve a design that fulfills certain requirements through multiple iterations, learning by doing.² The first step is designing a biological system that is expected to be able to perform the task. This is followed by building that design using DNA parts, and integrating them into a microbial chassis. When this is done, the system can be tested – using a variety of assays – to see if it is indeed suitable for the desired application. During this phase, a lot of data is collected through production- and omics-profiling. This is then used during the learn phase to influence the next design, as it is unlikely that the optimal system, demonstrating the right properties, is obtained the first time. Multiple iterations are usually required, and



so the learning phase relies on the ability to predict the biological systems behavior in response to a design change. Machine learning can be of great help here, statistically linking an input to an output, to predict the result for completely new scenarios.

MAKING THE COMPLEX EASY

Synthetic biology opens up many new possibilities, and its structured nature makes it easier to move forward toward new discoveries. However, although the principles are straightforward, the synthetic biology workflows are generally complex, and rely heavily on automation to achieve rapid and reproducible results. Without it, this new and exciting discipline would not be able to progress at a sufficient rate.

Higher and higher levels of automation can be seen in many labs all over the world, from handheld electronic pipettes that can aspirate and dispense several channels simultaneously, to fully automatic

liquid handling workstations powered by intelligent software that can follow the most complex protocols. Many laboratories that perform high throughput screening or clinical and analytical testing – as well as large-scale biorepositories – simply would not exist without this technology.

In addition, automation all but removes the human variability factor, increasing reproducibility and ensuring productivity through staff absences, labor issues, and a variety of other challenges.

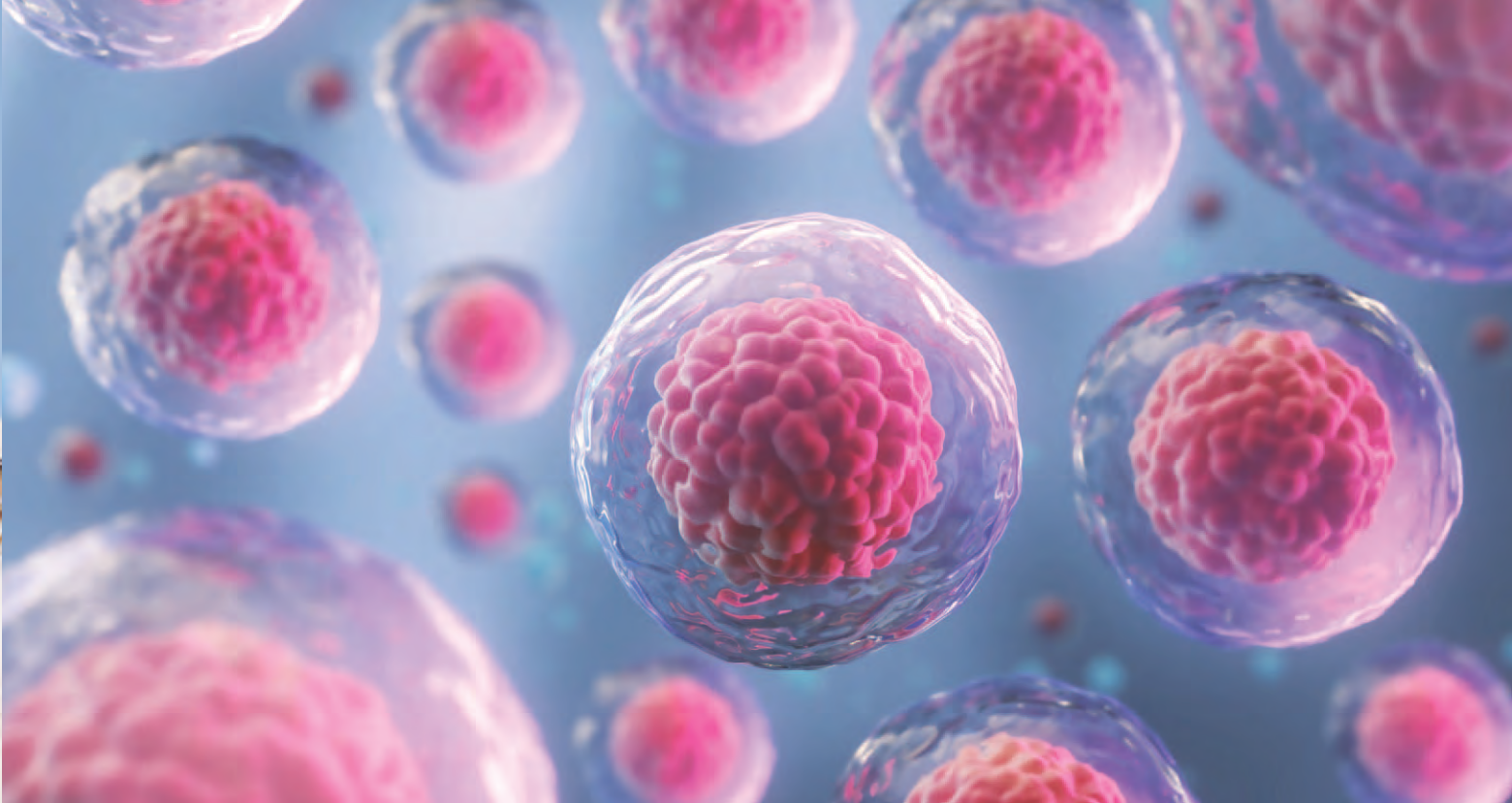
THE 3D PUZZLE

3D cellular models are becoming increasingly popular in drug discovery, providing more physiologically relevant results than 2D cell cultures or animal models. These microenvironments can more accurately mimic the complex immune response of human tissues, which is of great importance, helping to avoid costly late-stage failures of drugs in clinical trials. Grown using a variety of approaches, 3D

cell culture workflows are another example of research benefiting from automation.³ Automated solutions are required both for consistent growth of 3D cell cultures, and to support cell imaging and real-time cytometry assays for drug discovery because manually examining cells under a microscope is both labor intensive and time consuming. Automated culture maintenance and imaging improves reproducibility and throughput, as well as removing the risk of missing a key cellular event when leaving the lab – an important consideration for any cell-based study.

COLLECTIVE KNOWLEDGE

Many biological studies produce a tremendous amount of data, with thousands of genetic sequences produced daily. If not reused, this data will go to waste, together with all the possible insights that it could have provided.⁴ Considering the entire human genomic sequence only requires 1 GB of storage



space, this is truly a shame. Fortunately, it is becoming increasingly common for researchers to upload their data, providing open access to anyone who is interested. If shared in an effective and comprehensive way, this data can greatly increase the impact of the original experiments, making the most of something that took significant funding and research time to produce. By sharing sequencing data globally, initiatives such as the Darwin Tree of Life and the 100,000 Genomes projects are made possible.⁵ The former is a tribute to biodiversity, aiming to sequence the genomes of 70,000 species of eukaryotic organisms found in the UK, while the latter project uses data from patients affected by a rare disease or cancer, with the goal of advancing diagnosis and personalized treatment. Furthermore, giving open access to data also provides other benefits, such as increased credibility; if the research data is made available and possible to reproduce, it becomes more believable.

However, for others to make use of

data, it needs to be organized and documented properly. This type of careful cataloging of results is equally beneficial to groups that do not plan to upload their data because it promotes traceability and repeatability. There are many software platforms that work well with automated workflows to offer scientists a convenient way to plan experiments and manage results, as well as receive feedback on the outcomes. For example, the Synthace Life Sciences R&D Cloud allows scientists to automate experimentation and share insights. Berlin-based Labforward is another company offering increased lab connectivity, enabling scientists to effectively connect their devices to make research data more manageable and easily accessible. On the same note, a company in San Francisco called Benchling had developed a platform that helps standardize and centralize R&D data, accelerating and improving research while working seamlessly with third-party hardware. The software company Titian offers similar services, driving digitalization of research and advancing

management and traceability in every step of the sample lifecycle. Many of these advances are being made possible through the work of the SiLA Consortium, a non-profit industry body working to develop free and open system communication and data standards, providing researchers with an opportunity to connect, interface with their instruments, and merge data across the laboratories. These are only a few examples and, as more and more scientists grasp the benefits of laboratory digitalization, an even greater choice of solutions will become available.

SUMMARY

Automation is a great way to catapult laboratories into the future, speeding up sample preparation and establishing high throughput versions of complex workflows while minimizing the risk of cross contamination, eliminating human errors and saving time and resources. Automated solutions are particularly important to fields

such as synthetic biology, allowing the development of a more structured approach. This has enabled synthetic biology to become a powerful tool in drug discovery, replacing the hit-and-miss strategies commonly employed in many laboratories with the design-build-test-learn principle. This relatively new field is empowered by powerful machine learning software, which can make predictions based on large data sets that are beyond the capabilities of the human mind to quickly and easily comprehend. Driving science forward in such a structured manner helps speed up new discoveries and reduce the number of failed experiments.

Learning from our own mistakes can be of great help, but learning from the mistakes of others performing similar research in parallel is a far more powerful tool, as many laboratories around the world are currently discovering. There are several software platforms that have been developed especially for this purpose, helping scientists to document, store and share their data with others, as well as streamlining workflows through connectivity between programs and hardware. With so many tools available, digitalizing and immortalizing your research has never been easier, bringing about the laboratory of the future, which is not only fully digitalized, but connected to research centers around the globe, letting everyone reap the benefits of hard-won knowledge. ♦

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Luca Vallenggia is the Senior Vice President of Laboratory Automation and interim General Manager of the Genomics Reagents business at Tecan. Over the past decade, he has focused on driving innovation in lab automation and digitalization. He played a pivotal role in defining Tecan's product portfolio, and in commercializing some of the most successful lab automation solutions on the market. His passion for advancing research and scaling healthcare innovation has contributed to Tecan's growth strategy and leading position in the life sciences sector. He is a strong advocate of collaborative research, striving to leverage the potential of automation in new applications, from specialty immunodiagnostics to 3D cell culture and synthetic biology. He is also a driving force behind Tecan's digitalization strategy. He earned Masters degrees in Molecular Biology from the University of Basel, and Advanced Studies in Management, Technology and Economics from ETH Zurich, both in Switzerland.

EXTRACTABLES & LEACHABLES

Detecting the Unknown With Extractables & Leachables Analysis

By: Derek Wood, Xiaochun Yu, PhD, and Aaron Lamb

INTRODUCTION

Plastic is inextricably linked to drug development: the vast majority of drugs are manufactured in single-use technology utilizing plastic components, stored in primary or secondary plastic packaging, or delivered using plastic devices. This comes as no surprise. Plastic is highly practical, malleable, versatile, hygienic, and low cost, and it helps developers to meet safety standards and reduce the cost of manufacturing.

However, plastic polymers require additives to provide their desired properties. Because additives, such as plasticizers and UV absorbers, aren't chemically or physically bound to the polymers, they readily migrate from the process, container, packaging, or medical device into the drug product. This migration can create safety risks, including decreased drug stability, active ingredient inactivation, or increased toxicity, and can alter the taste, smell, or color of the drug product.

In the quest to accelerate drug development and improve drug safety, developers must also consider this more problematic side of the plastic revolution. Regulatory bodies are expecting a wider remit on toxicology risk assessments, recognizing that it is not just the drug that needs to be scrutinized but its packaging and manufacturing process too.¹ Extractables and leachables (E&L) testing is now required early on in toxicology risk assessments to identify and quantify toxic compounds of interest quickly and accurately.²

Established methodologies already exist for E&L testing, but they are often manual and time-consuming, leaving developers open to escalating costs and error-prone results with limited reproducibility. Developers must err on the side of caution, so every

tentative unknown requires an assumption of toxicity. But by falsely categorizing harmless compounds as toxins, whole devices or manufacturing processes may need unnecessary reworking, incurring costs and delays.

A new generation of extraction, identification, and quantification tools, now recognized as approved methods by regulatory bodies, are changing the E&L testing landscape. These methods, based on the latest sample preparation, separation, detection, and analysis technology, look set to cut testing times and related costs while improving result accuracy.³

THE CHALLENGING LANDSCAPE OF EXTRACTABLES & LEACHABLES ANALYSIS

Before we consider the challenges posed by E&L analysis, we must define testing terms. Extractables testing is a "worst-case-scenario" analysis performed on the containers surrounding a drug product: this might be the packaging, processing equipment, or storage solutions. Extreme levels of solvent concentration and/or heat are applied to evaluate the potential risk of chemicals migrating into the drug product, and the resulting extractables are then analyzed.

Leachables testing, however, is performed on the drug product itself. Although accelerated or forced conditions might be used to simulate the passage of time, the analysis aims to investigate compound migration from packaging or medical devices under normal clinical use.

Whatever the drug product and whichever part of the processes or packaging being examined, E&L analysis brings sev-

eral key challenges. First, leachables and extractables are often unknown compounds — and when these compounds migrate into drug formulations, they can interact with the drug product and form secondary leachables. In turn, these secondary leachables may only be identifiable after conducting stability studies on the drug product.

Second, when working with unknown compounds, surrogate standards are needed to estimate the concentration of the unspecified compounds. When using semi-quantitative methods to evaluate these unknown compounds, uncertainty factors are also required. Depending on the compound, some analytical techniques add more variability than others, and therefore, greater uncertainty. This can make it difficult to accurately quantify the compound of interest.

Finally, the decreasing limits of detection and limits of quantification needed for

certain types of compounds mean that part per billion (ppb) and sub-ppb detection requirements are not uncommon. Detection at this level can be challenging.

When working with evermore complex drug formulations, with many potential unknown extractables and leachables, these challenges can prevent accurate and timely detection. Traditional methods that depend largely on time-consuming, manual processes can introduce errors, as well as possible contamination. When quantitative results carry greater uncertainty due to these factors, scientists are forced to intentionally overestimate material or process toxicity to account for the uncertainty in reporting accuracy, which can result in unnecessary costs through process, packaging, or device redesign.

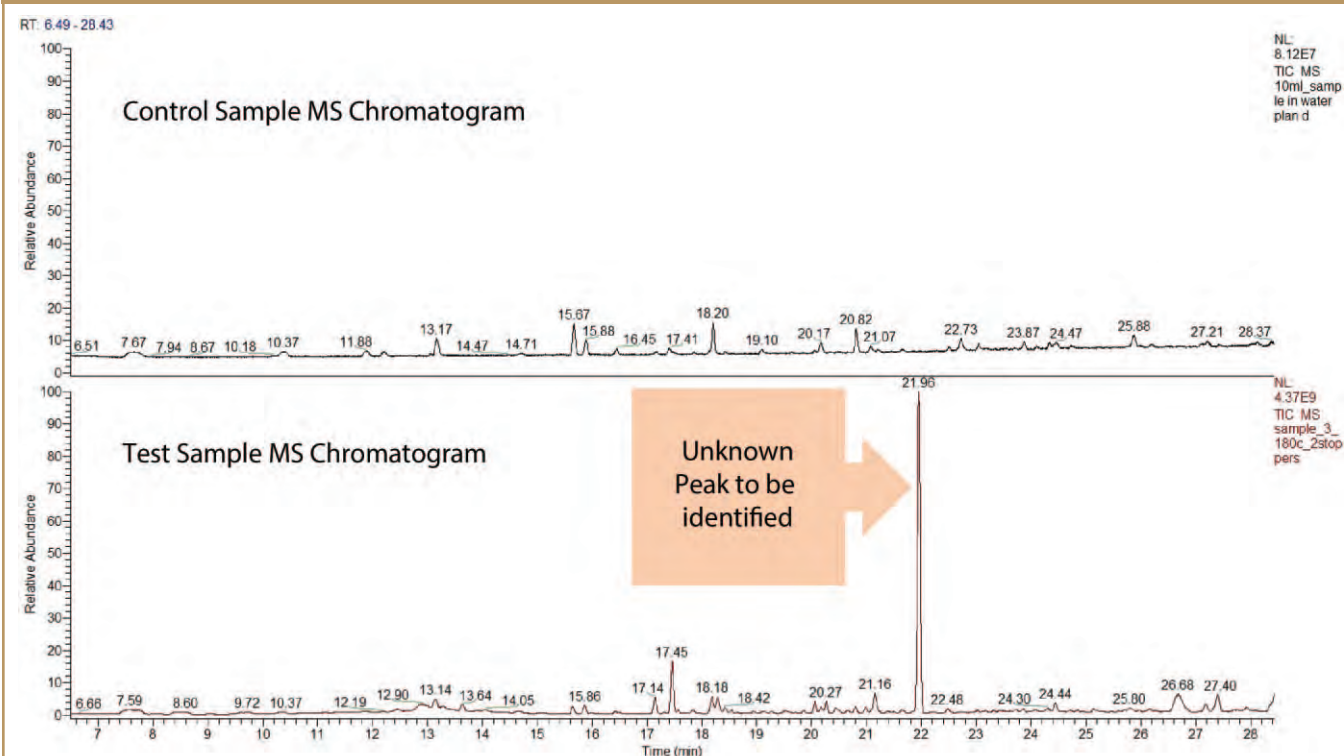
As regulatory requirements, such as the US Pharmacopeia USP 1663 and USP 1664 guidelines, continue to shift and evolve, automated techniques that can de-

liver the very highest levels of detection and quantification accuracy will become standard practice.^{4,5}

DELIVERING CONFIDENT RESULTS BY IMPROVING ANALYSIS ACCURACY & SPEED

New technologies, software, and workflows based on mass spectrometry (MS) are now being used for E&L analysis to enable faster and more accurate detection and quantification. These systems are highly automated and integrated, supporting the end-to-end workflow from sample extraction to detection, quantification, and analysis. The result: faster and more accurate analysis at a lower cost.

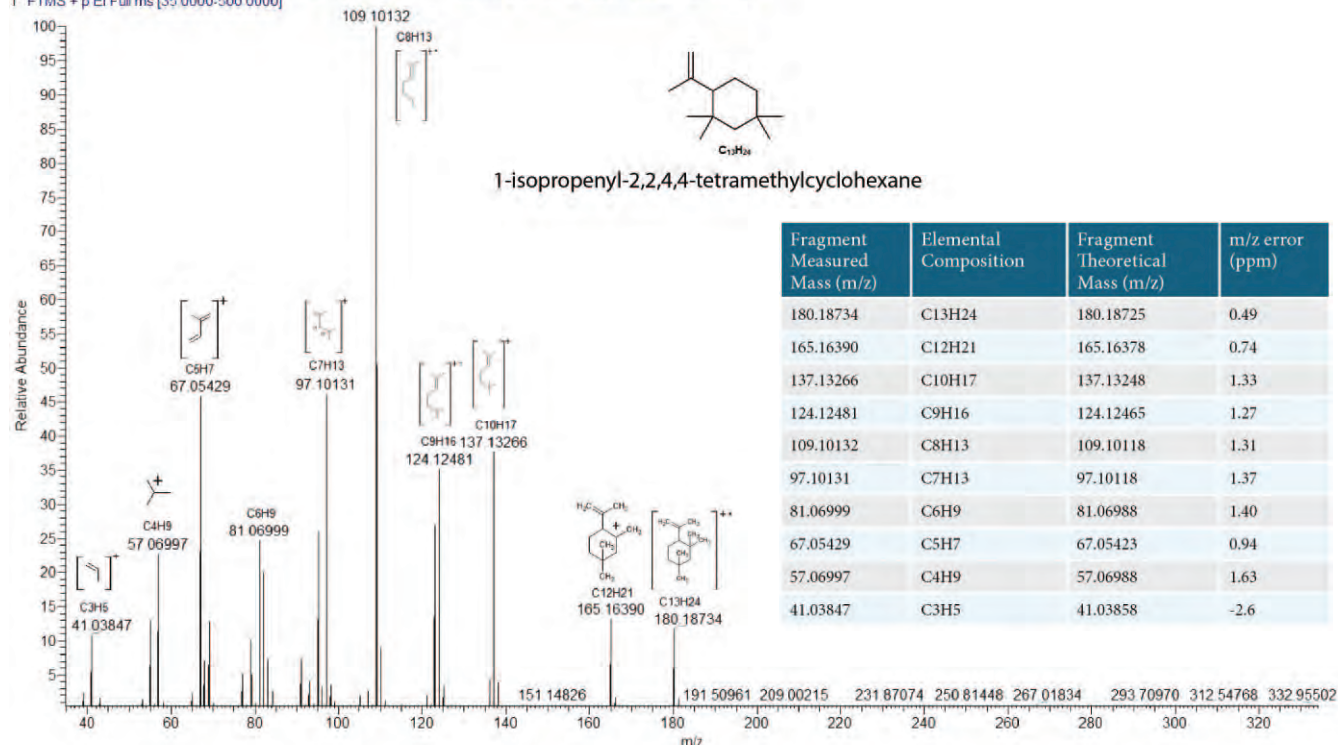
FIGURE 1



Thermo Scientific™ TriPlus™ 500 Headspace (HS) Autosampler with Thermo Scientific™ Q Exactive-Orbitrap GC-MS/MS analysis of a negative control sample (with E&L not present) versus a test sample showing an unknown peak in the MS chromatogram.

FIGURE 2

Sample_3_180C_2Stoppers#4869-4879 RT 21.93-21.98 AV: 11 SB: 55 21.77-21.87 22.08-22.22 NL: 5.94E8
T: FTMS + p EI Full ms [35.0000-500.0000]



Using the HRAM spectrum of the unknown peak shown in Figure 1, Thermo Scientific™ TraceFinder™ software was used to confirm the formula of each fragment and elucidate the unknown compound structure. This table reports the 1-isopropenyl-2,2,4,4-tetramethylcyclohexane fragments information and shows the high mass accuracy provided by the HRAM-MS technology, even for low masses (<100 m/z).

AUTOMATED SAMPLE EXTRACTION

Traditional methods of sample extraction use Soxhlet or solvent reflux to extract materials, but this is a highly manual process that offers poorly reproducible results, despite requiring the skills of specialized analysts. In addition, these techniques can take up to 24 hours to run and require large volumes of solvents, both of which increase costs and limit laboratory throughput.

Automated sample extraction (ASE) is often the first automated technology brought into the E&L analysis workflow. ASE systems use high pressure and high temperature to remove unwanted matrix components and decrease solvent viscosity. This accelerates the diffusion of the analyte into the solvent, helping to achieve

very low detection and quantification limits. For this reason, ASE technology is recommended by the PQRI and proposed as a viable method by USP 1663 and USP 1664.⁶⁻⁸

The most advanced ASE systems can automatically extract samples in as little as 15 minutes, using only 10 mL of solvent. These added practical benefits mean that costs are reduced, and analysts are provided with valuable walk-away time.

MULTI-TECHNOLOGY APPROACHES TO SEPARATION & DETECTION

A single sample of extractables or leachables can contain a wide range of unknown compounds of varying volatility. When analyzing unspecified compounds,

a surrogate standard is needed, but this introduces uncertainty. Therefore, an uncertainty factor is required to establish the analytical evaluation threshold (the level at which a potential toxin must be declared for a toxicology risk assessment). If the detection technique is well-matched to the compound or class of interest, then this uncertainty can be reduced.

The volatility of the compound generally determines the most effective method of separation and detection, and it makes sense to use a range of technologies for full determination.

Unknown leachable compounds may often be considered non-volatile. Liquid chromatography-mass spectrometry (LC-MS) is often the most effective technology for this separation and detection, especially when the LC element is coupled with high-resolution accurate mass (HRAM) sys-

tems. HRAM gives an accurate measure of the mass of ion fragments and this, in turn, helps to identify the compound.

Volatile or semi-volatile leachables, however, are best resolved with gas chromatography-mass spectrometry (GC-MS) systems, due to the technology's sensitivity and selectivity. Volatile and semi-volatile compounds may constitute a significant portion of the total potential leachables that may be present in a drug product, especially for dry powder products such as from packaging for dry-powder inhalers (DPIs) or for lyophilized products.⁹ Modern, capillary GC columns can offer increased peak capacity, which leads to excellent chromatographic resolution, along with enhanced reproducibility (Figures 1 and 2).¹⁰ Next-generation GC-MS systems can be coupled with simple sample preparation techniques, such as head-space sampling, that efficiently extract volatiles from heavier non-volatile matrix

compounds. This quick and simple sampling technique prevents contamination of the analytical system and leads to improved method robustness.

Elemental or organic leachables are often present at very low levels and thus require highly sensitive detection techniques. The latest inductively coupled plasma-mass spectrometry (ICP-MS) systems provide the level of resolution needed to reach even sub-ppb levels of detection.

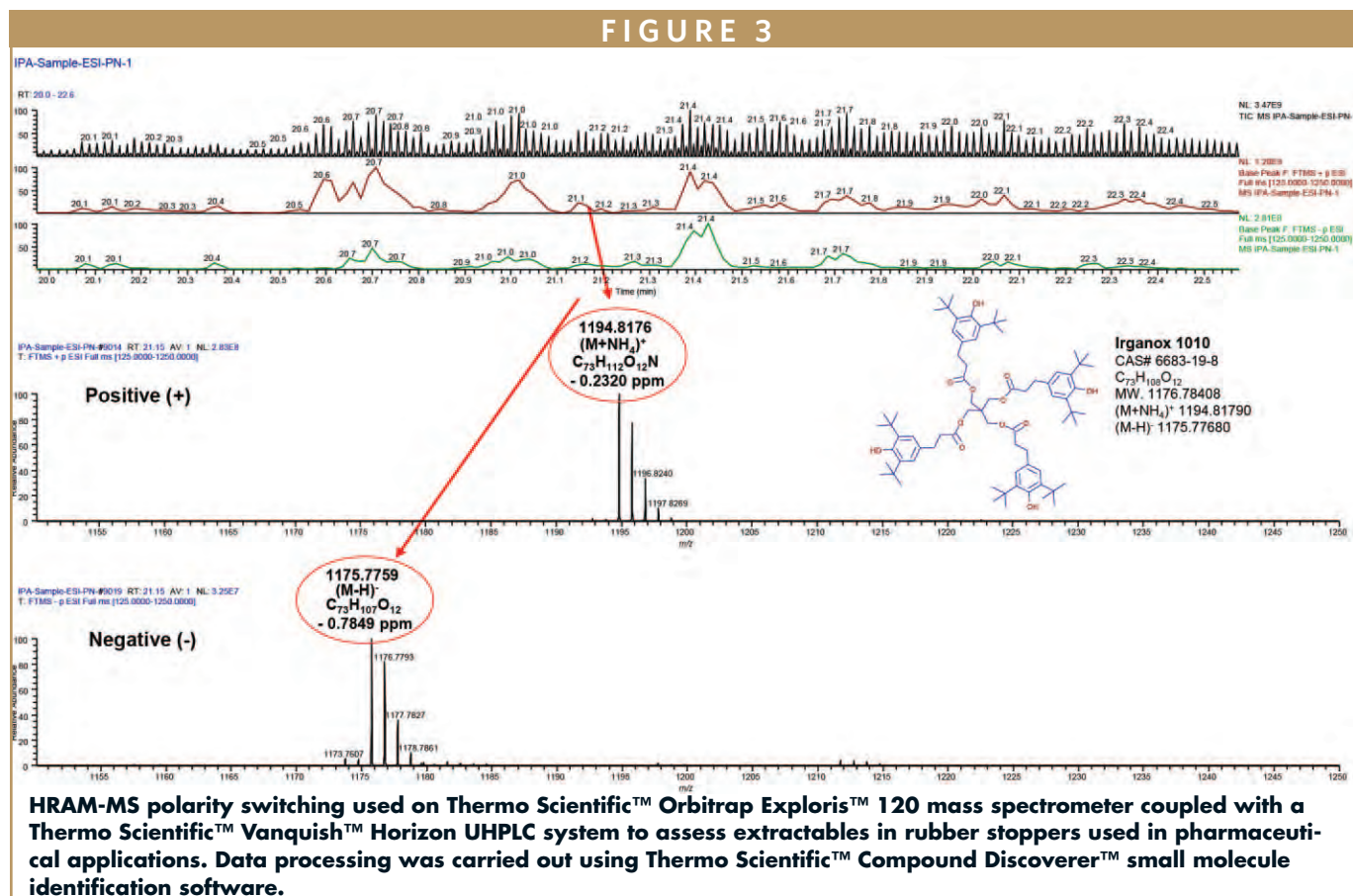
Alternatives to MS can also be used, such as charged aerosol detection (CAD), to quantify compounds with no ultraviolet chromophore, or diode array detection (DAD) to detect trace levels of semi- or non-volatile species. Another significant advantage of using CAD detection is that when it is used in combination with an inverse gradient, the detected signal is mass proportional, which negates the need for multiple expensive surrogate standards.

EXPANSIVE LIBRARIES & ADVANCED ANALYSIS

Automation software is becoming commonplace in the modern analytics laboratory, removing the manual operation of sample extraction, separation, and detection — and providing scientists with walkaway time to focus on value-added tasks. Now, advanced software is also being used to power sample analysis and provide deep insight into extractables profiles (Figure 2).

For example, HRAM-MS systems can be set to rapidly switch between positive and negative polarity modes to collect data with future use in mind (Figure 3).¹¹ The polarity needed for immediate analysis is achieved, but additional data for the opposite polarity is automatically collected for retrospective analysis at a future date. Gathering this and other fragmentation data from MS2 or MSn modes means that

FIGURE 3



crucial molecular fingerprint information can be collected to aid structure identification and the elucidation of unknown entities.

Many chromatography and MS systems now automatically integrate with comprehensive spectral libraries to aid compound identification and enable them to be rapidly characterized.

E&L ANALYSIS: A POWERFUL ENABLER FOR FASTER & SAFER DRUG DEVELOPMENT

Plastics and their additives are certainly here to stay: the safety, speed, and economies they offer are simply too important to drug developers and the patients they serve. So, as drug developers look to bring new therapies to market quicker and most cost-effectively, E&L analysis will become an ever more important part of that process. Regulatory requirements will continue to evolve, and E&L analysis will need to continue to keep pace, providing that all-important first step toward full toxicology risk assessment.

By investing in the latest technology and software, analytical laboratories can ensure they meet these stringent requirements today, immediately reaping the benefits of speed, accuracy, and efficiency offered by automated systems while keeping pace as regulations morph and evolve.

This investment will help E&L analysis become an enabling part of the pathway as drug developers continue to strive to bring drugs to market faster and more safely. Modern techniques will help to ensure drug safety and efficacy, free from the effects of the manufacturing process, packaging, and delivery mechanism. ♦

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BIOGRAPHIES



Derek Wood is a Senior Principal Scientist at PPD, part of Thermo Fisher Scientific. He earned his Bachelor of Science degree in Biochemistry and has over 30 years of pharmaceutical CRO experience, including 21 years at PPD, where he has served in various positions of scientific and business leadership. Most of his time at PPD has been focused on contributing to PPD's extractable and leachable (E&L)

testing services, a premier service provider of E&L consultation, study design, analytical testing, and toxicity evaluation.



Dr. Xiaochun Yu is a Senior Principal Scientist at PPD, part of Thermo Fisher Scientific. He earned his PhD in Chemistry and has over 20 years of experience in the pharmaceutical industry and over 10 years of experience in academic research in polymer chemistry. He has been leading extractables and leachables (E&L) study since 2003, providing scientific leadership, technical and

regulatory guidance to the team and clients for the design and execution of E&L programs. His team has successfully completed hundreds of E&L studies for numerous drug products, including pMDI, DPI, parenteral, ophthalmic, transdermal, and oral dosage forms as well as medical device and drug/device combination products. In the past few years, there have been at least 30 drug products approved with E&L studies completed by his team.



Aaron Lamb is a Pharma and Biopharma Market Development Manager working in the Chromatography and Mass Spectrometry division at Thermo Fisher Scientific, UK. He collaborates with pharmaceutical manufactures and analytical testing labs and is responsible for generating collateral and the planning of pharma campaigns. He has also worked in industry as an

R&D and Pharma Team Leader at Intertek using a multitude of analytical techniques including ion chromatography, GC-MS, and LC-MS in healthcare and pharmaceutical analyses.

CLINICAL TRIALS

New Technology & the Global COVID Pandemic Drive the Need for More Decentralized Trials

By: Suhas Gudihal, MS, MBA

Remote clinical trials are becoming the new standard in clinical research. A variety of terms have been used to describe remote trials that incorporate patient-facing technologies, such as tablets, smartphone apps, or wearable sensors. They have been described as virtual trials, decentralized trials, remote trials, direct-to-patient trials, siteless trials, and hybrid trials. Whereas a digital trial is defined by the method used to capture the clinical trial data, a true digital clinical trial is one in which all data are captured without the use of any paper forms during the conduct of the study.

The COVID-19 pandemic has accelerated the ongoing shift to remote clinical trial monitoring. Remote site access and monitoring platforms are now an essential element of the clinical trial process and a vital connection between the sponsor, the clinical research organization (CRO), and the research site.

REMOTE CLINICAL TRIALS – KEY BENEFITS TO SPONSORS & PATIENTS

By digitizing the entire clinical trial process, remote clinical trial monitoring is becoming critically important to both sponsors and trial site administrators, offering the following benefits:

Complete access to remote clinical trial sites - By digitally connecting sponsor and trial site systems, the clinical trial administrator can securely access the site's documentation from anywhere at any time. Sponsors and CRO monitors can securely access sites that they need to manage. This secured access allows monitors to complete their work remotely without onsite restrictions, saving considerable time and reducing overall cost.

Site and sponsor communication - The digitization of clinical trials allows for streamlined communication in the form of trial alerts and notifications, real-time dashboards, messaging, and email push notifications. These features improve communications and consolidate all conversations in which the work gets done – in the system itself.

Process compliance and trial oversight - The digitization of clinical trials creates a secure environment in which to comply with both HIPAA and 21 CFR Part 11 regulations. Built-in audit trails and the ability to view and verify trial documents provide a path to compliance. Adaptive data integration is used to integrate heterogeneous systems data. The ideal environment delivers "defense of depth" security, whereby security is controlled from a physical structure, such as entry to data centers, hardening networks, and servers. When it comes to application, implementing security at the user interface (UI), business, and data access layer component (DALC) levels enables data protection via concentric layers of security.

Automated workflows and repeatable standardized processes - With the digitization of clinical trial systems, the documents needed for submission to FDA and the workflow for review and approval can be automated. All trial documents are stored centrally and streamlined with secured access to all privileged users. With digitization, routing of documents is automated via a unified platform that allows administrators to easily redact, edit, and capture data as well as update versions of documents in a single database. The industry is moving toward a unified platform with a single database for all clinical trial products like electronic data capture (EDC), clinical trial management systems (CTMS), elec-

tronic trial master files (eTMFs), and electronic patient-reported outcomes (ePRO).

Easy tracking of study progress and trial sites - Digitization helps improve site performance and enables real-time tracking of study progress without site staff assistance. System alerts and notifications for document completion and other site activity can be easily set up for comprehensive tracking. Analytics with dashboards can provide a singular view of site efficiency, study timelines, document completion, and outstanding actions to manage trial activities more effectively.

THE EVOLUTION OF REMOTE CLINICAL TRIALS

Remote/virtual clinical trials have increased in popularity since the start of the COVID-19 pandemic, in response to the adaptations and the contingency plans that

every industry, including the life sciences, have had to implement.

The technological advances made throughout the past 5 years have made remote clinical trials possible. With the technology tools available today, remote/virtual clinical trials bring clinical research directly into the participant's home via a central and virtual coordinating site.

Remote clinical trials utilize devices that monitor and deliver vital information about patients. Wearables like Apple Watch, Fitbit, electrocardiogram (EKG) monitors, blood pressure monitors, and glucose monitors are also used to get a complete picture of the patient's health.

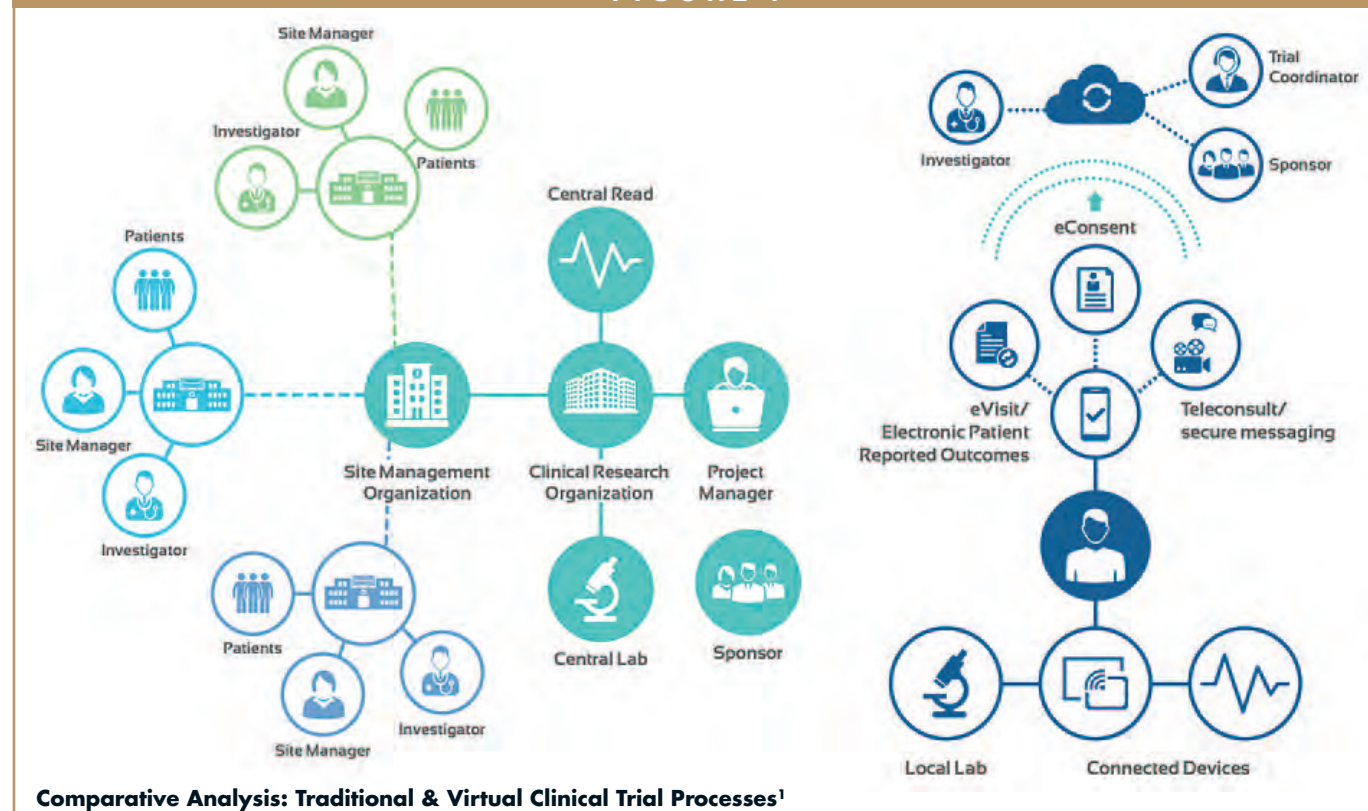
Mobile health applications and telehealth technologies are used to collect medical data from participants and transmit this information to the central study center. Video conferencing has revolutionized the ability to remotely monitor and engage with patients and clinical trial

managers. Clinical trial research companies believe the use of patient-facing technology helps in widening the pool of trial participants/volunteers, enhancing patient retention, improving data quality, and fostering a holistic, patient-centric experience. Patient-facing systems are designed to provide a wide range of computer- or internet-based services that support patient interactions with the healthcare system. Examples of these systems include patient portals, mobile applications, and online peer support communities.

The need for remote clinical trials is increasing because:

- Remote clinical trial solutions can significantly improve recruitment of patients and site staff, safety monitoring, patient education, pre-screening, and data verifications.
- Remote trials can deliver significant cost efficiencies to pharmaceutical and biotechnology companies, positively im-

FIGURE 1



pacting their bottom lines.

- Implementation of decentralized and remote solutions also accelerates time-to-market for new drugs by reducing the overall length of the clinical trial life cycle. Other benefits include reduced enrollment periods, faster study initiations, lowered patient dropout rates, and improved data collection features.
- Remote visit set-ups can reduce the overall cost of conducting virtual clinical trials, compared to conventional clinical trial methods. Additional capital savings can result from the reduced number of operational clinical sites and lower patient travel reimbursements.

TECHNOLOGY IMPROVES THE EFFECTIVENESS OF REMOTE CLINICAL TRIALS

The growth of decentralized clinical trials is being enabled by several key technologies that span the entire clinical trial spectrum. Notable technology enablers include the following:

Patient-facing technologies - In remote clinical trials, patients need to be provided with choices related to accessing trial information, user-friendly training materials, video visits, and direct-to-patient study supplies, among other options. The availability of technologies that enable these choices can optimize a patient's clinical trial experience, which is especially important to the overall success of any remote clinical trial.

Unified data platform - With the advent of data lakes and unified data platforms that support the entire life cycle of clinical

trials, the effectiveness of decentralized trials has improved vastly. In decentralized trials, there is a variety of data sources, including devices, imaging technologies, electronic health records (EHRs), laboratory information systems (LIS), EDC, CTMS, and ePRO. Data platforms allow for real-time/remote access to all clinical trial data, and enable the deployment of automated and intelligent processes to provide near real-time data review. In addition, data platforms can facilitate the following:

- Real-time compliance monitoring to understand data completeness
- Data monitoring for safety
- Monitoring for data quality and completeness

On-site/remote consent from patients - Electronic automation of the patient consent process can enable flexibility and consistency in information exchange and data capture. The digitization of remote clinical trials provides easy-to-understand information and the ability to access consent information throughout a trial, ensuring appropriate regulatory compliance.

Clinical trial protocol development and design capabilities - The protocol is the playbook for any clinical trial. The advent of technologies that can connect patients remotely to trial sites can enhance the sponsor's understanding of site and patient burden during protocol development and design, and can help determine the appropriate level of "decentralization" within a specific trial, increasing its overall probability of success.

ARTIFICIAL INTELLIGENCE ACCELERATES REMOTE CLINICAL TRIALS

In the past few years, technologies like artificial intelligence (AI), machine learning (ML), and natural language processing (NLP) have made an enormous impact across all aspects of clinical research.

Advanced analytics tools that use AI and ML are providing clinical trial administrators the power to make sense of the vast amounts of data collected through clinical trials. These tools enable advanced statistical predictive modeling and process automation to enhance overall study quality.

Today, the volume, variety, and velocity of structured and unstructured data generated by clinical trials are outpacing traditional data management processes. The reality is that there is simply too much data coming from too many sources to be manageable by human teams alone. At Anju Software, we are constantly innovating tools, such as TrialMaster, an intuitive EDC suite that accelerates Phase 1-4 clinical trials and delivers features to drive decentralized trials. TrialMaster improves efficiencies and reduces workflow impact while enhancing data quality, resulting in faster study submission times.

As the remote clinical trial environment continues to evolve, AI/ML technologies show remarkable potential to automate data standardization while ensuring quality control, in turn easing the burden on researchers with minimal manual intervention.

The use of AI/ML-driven data management does more than accelerate data capture or provide generalized insights. These platforms seamlessly integrate large

volumes of data from a breadth of sources and feature automation tools to streamline the review process. They can also clean and house all data in a single location and use custom ML algorithms to identify data errors, outliers, and false entries. As a subset of AI, NLP can identify site- or study-specific risks in both structured and unstructured data.

AI/ML technologies also enable predictive analytics that can maintain patient safety and improve site performance by detecting and mitigating potential safety issues. They can also facilitate site selection, more effective risk-based quality management, enhanced patient recruitment and engagement, and overall efficiency throughout the clinical trial life cycle.

AI and ML cannot solve every problem in clinical research. However, AI/ML tools can increase the amount of data collected, pull from multiple data sources, and ensure the “cleanliness” of data for researchers to properly analyze. In a few hours, these tools can accomplish tasks that would take human researchers months or even years. In short, as the industry leaps into new frontiers, AI/ML strategies are redefining the clinical development cycle like never before. With digital transformation leading the way, drug companies can redouble their efforts to get to the right therapies into the hands of patients faster, yielding advances that will revolutionize the space forever. ♦

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BIOGRAPHY



Suhas Gudihal is Co-Founder, Anju Software, where he drives product strategy and direction as well as oversees Anju's technology architecture and product development. Throughout his career, he has created and managed product engineering labs across various environments. He has successfully built and scaled up engineering teams for start-ups to large enterprises. He has successfully integrated over 20 acquired companies. He oversees Anju teams responsible for the development and commercialization of adaptive technologies for clinical trials, medical affairs, and data with world-class customer support.

Leveraging AI and data-driven analytics, Anju's leading suite of solutions, including TrialMaster, delivers data and application integration capabilities to the global pharmaceutical, biotech, and contract research Life Sciences markets. He earned his BS in EE, his MS in Computer Systems, and his MBA with specializations in High Technology and Innovation. He is also a Certified Management Accountant of the IMA, and a Fellow of Management Accountant institute of India.

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PAN-VARIANT INHIBITORS

How Pan-Variant Inhibition Can Outsmart Cancer Treatment Resistance

By: Tim Clackson, PhD

INTRODUCTION

In targeted oncology, treatment resistance remains a pernicious obstacle to providing patients with therapies that confer lasting benefit. In certain types of cancer, tumors tend to develop mutations that render the cancer unresponsive to currently available targeted therapies, forcing the patient to move to a subsequent line of therapy. Their tumor can often out-mutate every targeted therapy available, one after another, until no effective treatment options remain. At that point, the cancer is free to progress unchecked, and the patient may succumb to their disease.

Fortunately, for many types of cancer in which such serial mutation is common, it is possible to develop targeted therapies that outsmart treatment resistance. The key is to anticipate the finite set of mutations that tend to emerge in a given cancer type, and to develop a single inhibitory agent that binds its target and maintains its anti-cancer activity regardless of the presence of any of those mutations.

To understand how we do that, it's important to first understand how treatment resistance emerges and why it's crucial to address in order to successfully treat cancer.

CANCER CELL MUTATIONS CAN LEAD TO TREATMENT RESISTANCE

As tumor cells proliferate, they tend to develop mutations more frequently than healthy cells. Some of those mutations confer resistance to certain treatments and are thus termed resistance

mutations. These mutations are distinct from activating mutations that drive tumorigenesis in the first place. Resistance mutations often occur at a therapeutic molecule's binding site on its target protein, such that the molecule can no longer bind to and inhibit its target. The set of resistance mutations a given cancer tends to develop in response to prior therapies is finite, and the sequences and positions of those mutations are often known empirically.

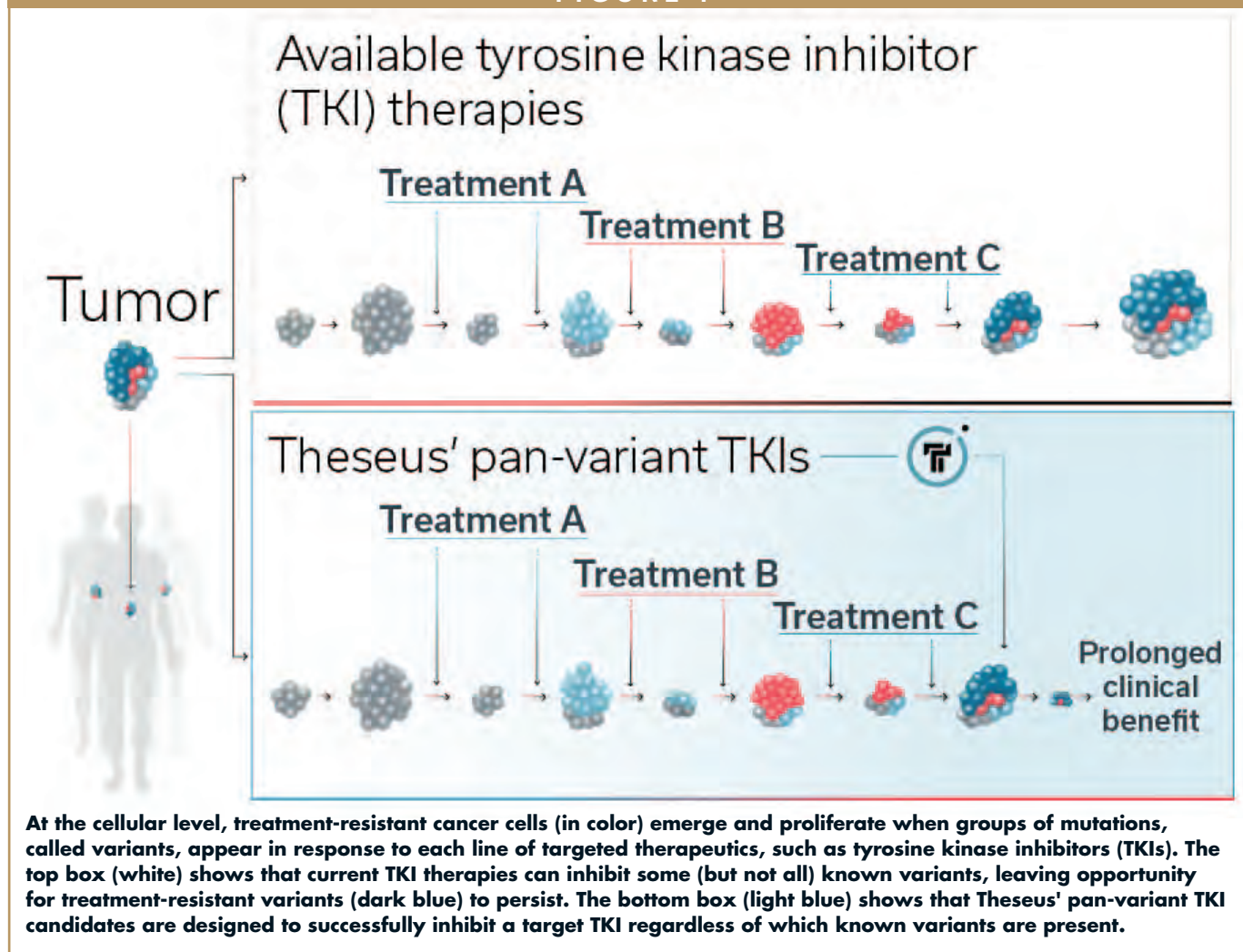
Resistance mutations can often be highly heterogenous — not only between patients, but within individual tumors. As a tumor grows, its dividing cells may partition into distinct clusters of genetically identical cell populations in which each clonal cluster is descended from a different parent cell with a slightly different genome, including perhaps a different collection of resistance mutations.

Additionally, a tumor's profile of resistance mutations will vary over time as well as space. Tumors tend to accrue new mutations without shedding old ones throughout the course of a patient's lifetime, and the patient's population of tumor subclones will often grow and shrink in response to the selective pressures of different targeted therapies. Cells with mutations that confer a selective advantage to the tumor (ie, resistance to the therapy) tend to proliferate more than other cells and occupy larger shares of the tumor's volume. Cell populations sensitive to the therapy tend to shrink.

So, what does this look like in the clinic? Resistance mutations' heterogeneity makes them difficult for physicians to both detect and to treat.

Treating resistance mutations after they have emerged is difficult because using a targeted therapy against the most recently emerged mutation is often only temporarily effective until the next

FIGURE 1



mutation occurs.

An often-futile arms race ensues: when a tumor being treated with first-line targeted therapy develops a resistance mutation, a physician moves on to the second-line therapy, to which the tumor may be sensitive, but only until the tumor ultimately develops another mutation that thwarts the second therapy's effect, and so on through a dwindling arsenal of therapeutic options until none remain.

Without therapies that can remain effective in the face of any mutation the cancer might develop, the patient remains perpetually vulnerable to disease progression.

HOW PAN-VARIANT INHIBITION CAN OUTSMART CANCER TREATMENT RESISTANCE

The answer to all these challenges lies in pan-variant inhibition. Pan-variant inhibitors are single therapeutic agents that bind a single target protein to inhibit cancer cell function, and maintain their anti-cancer activity in the face of all major classes of activating and resistance mutations. ("Variant" refers to each of the many possible combinations of resistance mutations that the protein might harbor.)

The goal in targeted oncology is to achieve pan-variant inhibition and, ideally, pan-variant inhibition should be accomplished with a single agent, avoiding

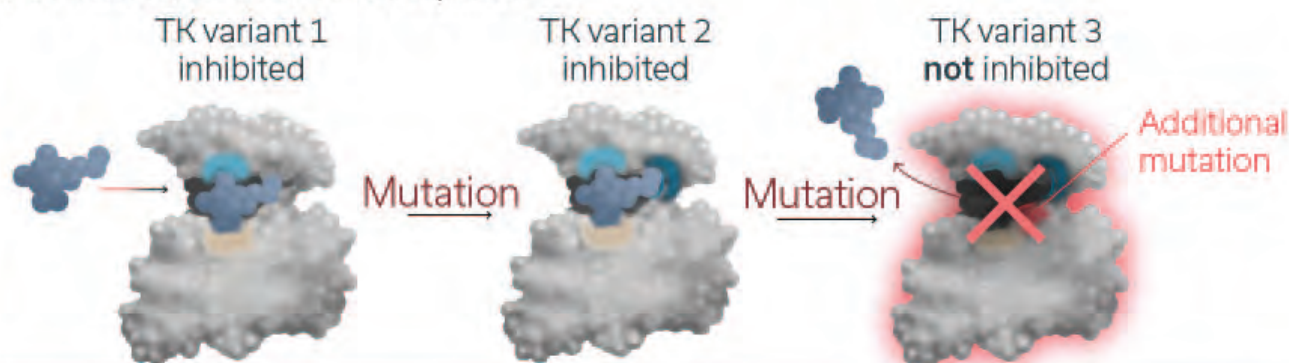
the potential complications and toxicities of drug combinations.

Pan-variant inhibitors simultaneously cut off all the tumor's routes to treatment escape via that target protein, so they can both suppress the emergence of resistance mutations during early lines of therapy, and address those mutations after they have already emerged during later lines of therapy. Thus, they have the potential to provide substantial benefit to patients in both earlier and later lines of therapy relative to current standards of care.

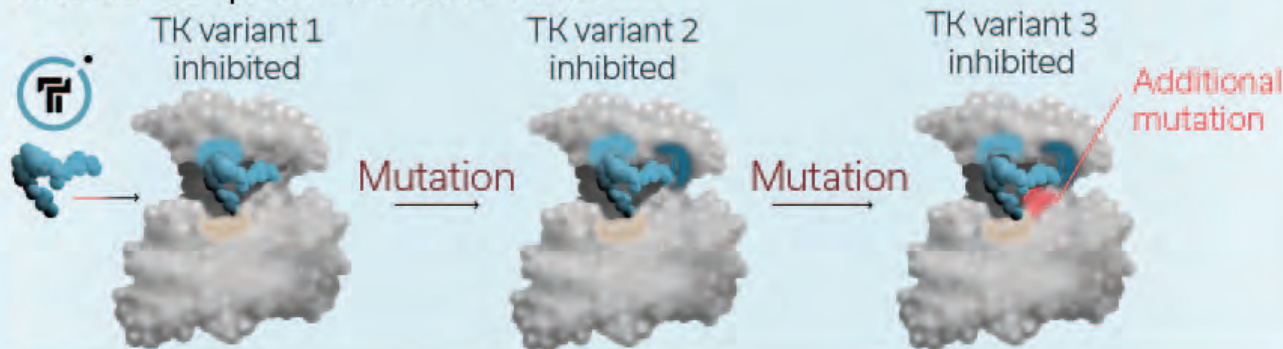
Fortunately, for several cancers prone to treatment resistance, researchers already have a deep understanding of the universe of resistance mutations that emerge in response to current therapies.

FIGURE 2

Available TKI therapies



Theseus' pan-variant TKIs



At the subcellular level, this figure shows that (top box, white) in the setting of existing TKI therapies, at least one of the target TKI's known variants (shown as different versions of a gray TKI, each bearing different combinations of colored mutations) prevents the therapeutic from binding, which confers treatment resistance to the cancer cell. The bottom box (light blue) demonstrates that Theseus' pan-variant TKIs can bind to and inhibit their target TKI in the setting of any known variant.

In many cases, they have also determined the three-dimensional molecular structures of these proteins, so we can visualize the shape of the protein's surface, identify binding sites for inhibitory molecules, and infer how known mutations might affect the shape of those binding sites.

THESEUS' APPROACH TO PAN-VARIANT INHIBITION

With this knowledge in hand, we at Theseus apply specialized techniques refined over decades of prior drug development to develop truly pan-variant inhibitors that have the potential to outsmart cancer resistance.

Theseus focuses on inhibiting tyrosine kinases (TKs), a family of enzymes that add phosphate groups to the amino acid tyrosine. This process is fundamental in regulating essential cellular processes, including cell proliferation and cell death, so mutations in tyrosine kinases can contribute to cancer development and progression. In fact, many cancers are driven largely by mutations that accumulate in single tyrosine kinases.

We begin developing a pan-variant tyrosine kinase inhibitor (TKI) candidate by identifying a specific tyrosine kinase that is known to accrue activating and resistance mutations in a given type of cancer.

Next, we use a carefully honed iterative process that optimizes the inhibitory

activity of the candidate molecule against all known classes of activating and resistance mutations that particular tyrosine kinase can harbor. Alternating between rounds of structure-guided, in silico molecule design and in vitro activity validation, we refine the molecule's structure at each iteration until we have optimized pan-variant TKI activity.

We validate the candidate molecule's inhibitory activity empirically against its target TK using Theseus' specialized Predictive Resistance Assay (PRA). The cell-based assay, honed over many years by the Theseus team, identifies inhibitors that show pan-variant coverage, ie, a broad range of activity against known activating and resistance mutations in a given can-

cer. The PRA involves evaluating candidate molecules in a large panel of cell lines in optimized conditions that mimic the human physiological environment. Each cell line harbors a specific resistance mutation of interest. The PRA provides a high-confidence way of assessing whether a given mutation is likely to be inhibited by the candidate molecule in patients.

THESEUS' PAN-VARIANT INHIBITOR MOLECULES

Since Theseus' founding in 2017, we have progressed our lead asset into the clinic, where it is being evaluated in gastrointestinal stromal tumors (GIST).

GIST is the most common sarcoma of the gastrointestinal tract with an estimated 4,000 to 6,000 new cases diagnosed in the US each year. About 80% of GIST cases are driven by activating mutations in a tyrosine kinase called KIT, and the disease remains KIT-dependent through successive lines of therapy. Patients typically receive first-line KIT-targeted therapy for GIST, but they often experience disease progression later due to the emergence of other resistance mutations in KIT, which render subsequent lines of targeted therapy significantly less effective. Current standards of care can address some, but not all, of these mutations, leaving an opportunity for GIST patients' tumors to develop resistance to treatment.

Our candidate in GIST, THE-630, is a small molecule, orally available pan-variant KIT inhibitor, intended for patients whose GIST has become resistant to previous lines of targeted therapy.

Based on our use of the PRA in designing THE-630, the molecule is predicted to achieve pan-inhibition of

cancer-causing mutations and resistance mutations known to occur in KIT in the setting of GIST.1 THE-630 will initially be under clinical evaluation for advanced KIT-driven GIST in both the fifth line (for patients who have progressed on prior lines of therapy) and the second line (an earlier stage setting in which there is the potential to interrupt the emergence of resistance mutations).

Our second program is THE-349, a fourth-generation, potent, and selective small molecule designed to inhibit all major classes of epidermal growth factor receptor (EGFR) activating and resistance mutations for the treatment of non-small cell lung cancer (NSCLC).

NSCLC is the most common form of lung cancer, accounting for approximately 85% of the estimated 2.2 million cases of lung cancer diagnosed globally in 2020. Activating mutations in EGFR occur in 10%-15% of Caucasian and up to 50% of Asian NSCLC patients, with up to 90% of those mutations found in exons 19 and 21. In response to treatment, patients' tumors can develop one or more additional EGFR mutations, causing resistance and rendering current therapies ineffective.

We have demonstrated preclinically that pan-variant inhibition of all major single-, double-, and triple-mutant EGFR variants, including those with the T790M and C797X mutations, with mutant-selectivity and central nervous system (CNS) activity, can be achieved with a single molecule.

Finally, Theseus is also developing a series of next-generation, pan-variant TKI molecules targeting BCR-ABL mutations for the treatment of refractory chronic myeloid leukemia and front-line Philadelphia chromosome-positive acute lymphoblastic leukemia. ♦

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BIOGRAPHY



Dr. Tim Clarkson is President and Chief Executive Officer of Theseus Pharmaceuticals. He most recently served as President and Chief Technology Officer at Xilio Therapeutics, where he led the development of the company's technology and product strategy. From 1994 to 2018, he was with ARIAD Pharmaceuticals, where he was President of Research & Development and Chief Scientific Officer. He played a key role in the company's evolution from early research to a global commercial oncology company, and its subsequent acquisition by Takeda. He led the multi-disciplinary R&D team that internally discovered and developed five clinical-stage product candidates, including ICLUSIG® (ponatinib), approved for patients with treatment-resistant Ph+ leukemias; ALUNBRIG® (brigatinib), approved for ALK+ non-small cell lung cancer (NSCLC); and EXKIVITY® (mobocertinib), approved for EGFR Exon20 insertion+ NSCLC. Prior to ARIAD, he was a post-doctoral research fellow at Genentech. He earned his PhD in Biology from the University of Cambridge, and his BA in Biochemistry from the University of Oxford. He serves as a Director on the boards of Forma Therapeutics, Elevation Oncology, and the Massachusetts Biotechnology Council (MassBio).

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CONTRACT MANUFACTURING



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Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization, with sites in Belgium, United States, Japan, and India, providing comprehensive process development services, cGMP manufacturing and drug product fill finish services of small molecule and large molecule APIs and intermediates. Ajinomoto Bio-Pharma Services offers a broad range of innovative platforms and capabilities to rapidly scale from clinical and pilot programs to commercial quantities, including: Corynex technologies, oligonucleotide synthesis, high potency APIs (HPAPI), biocatalysis, continuous flow manufacturing, and more. Ajinomoto Bio-Pharma Services is dedicated to providing a high level of quality and service to meet our clients' needs. For more information, contact Ajinomoto Bio-Pharma Services at www.AjiBio-Pharma.com.

CDMO SERVICES



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Technology & Services SHOWCASE

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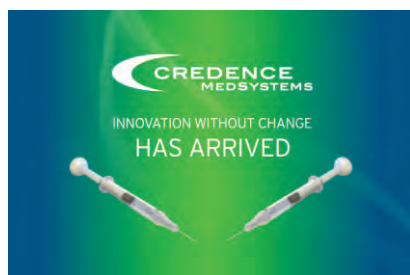
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Technology & Services SHOWCASE

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PRECLINICAL CRO

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GLOBAL DATA & ANALYTICS



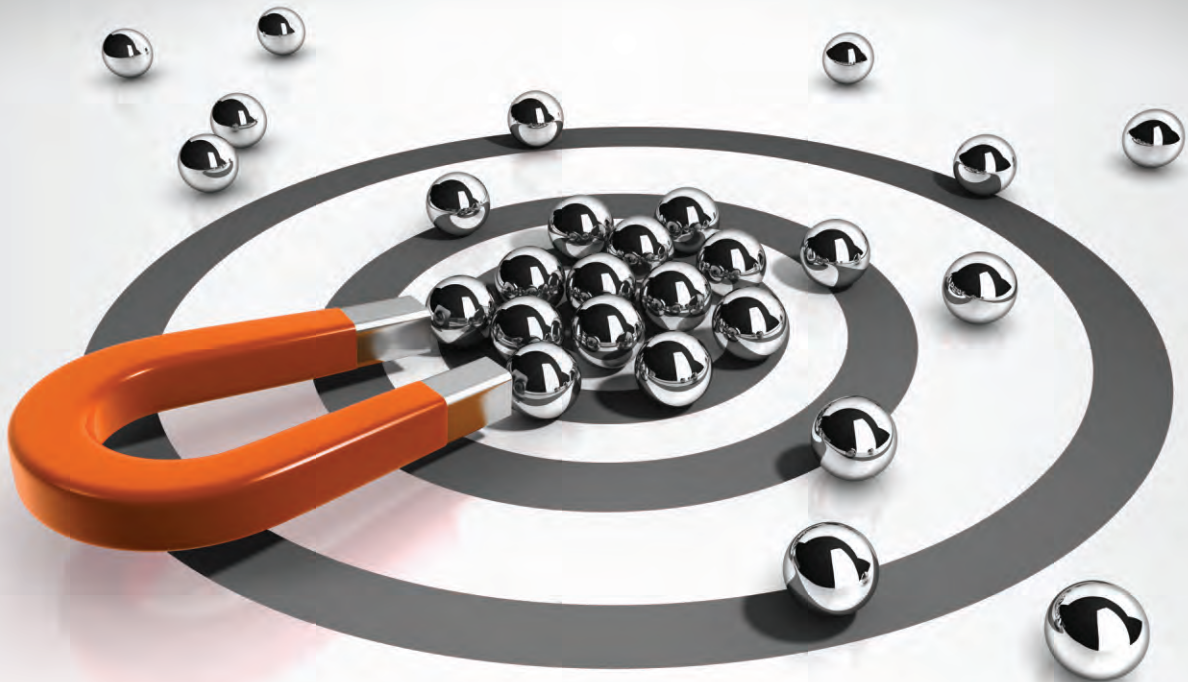
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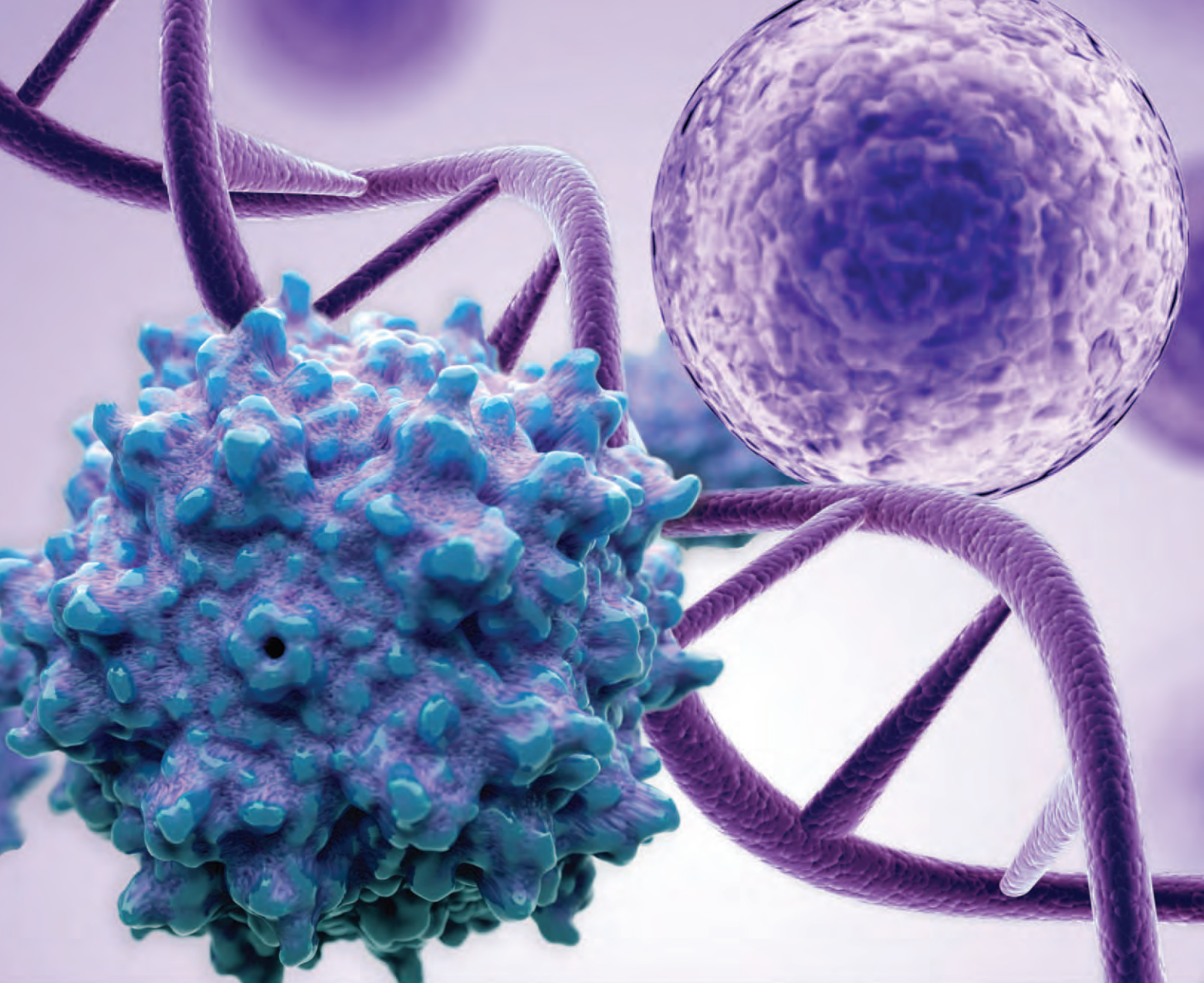


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