Drug Development & Delivery

January/February 2022 Vol 22 No 1 www.drug-dev.com

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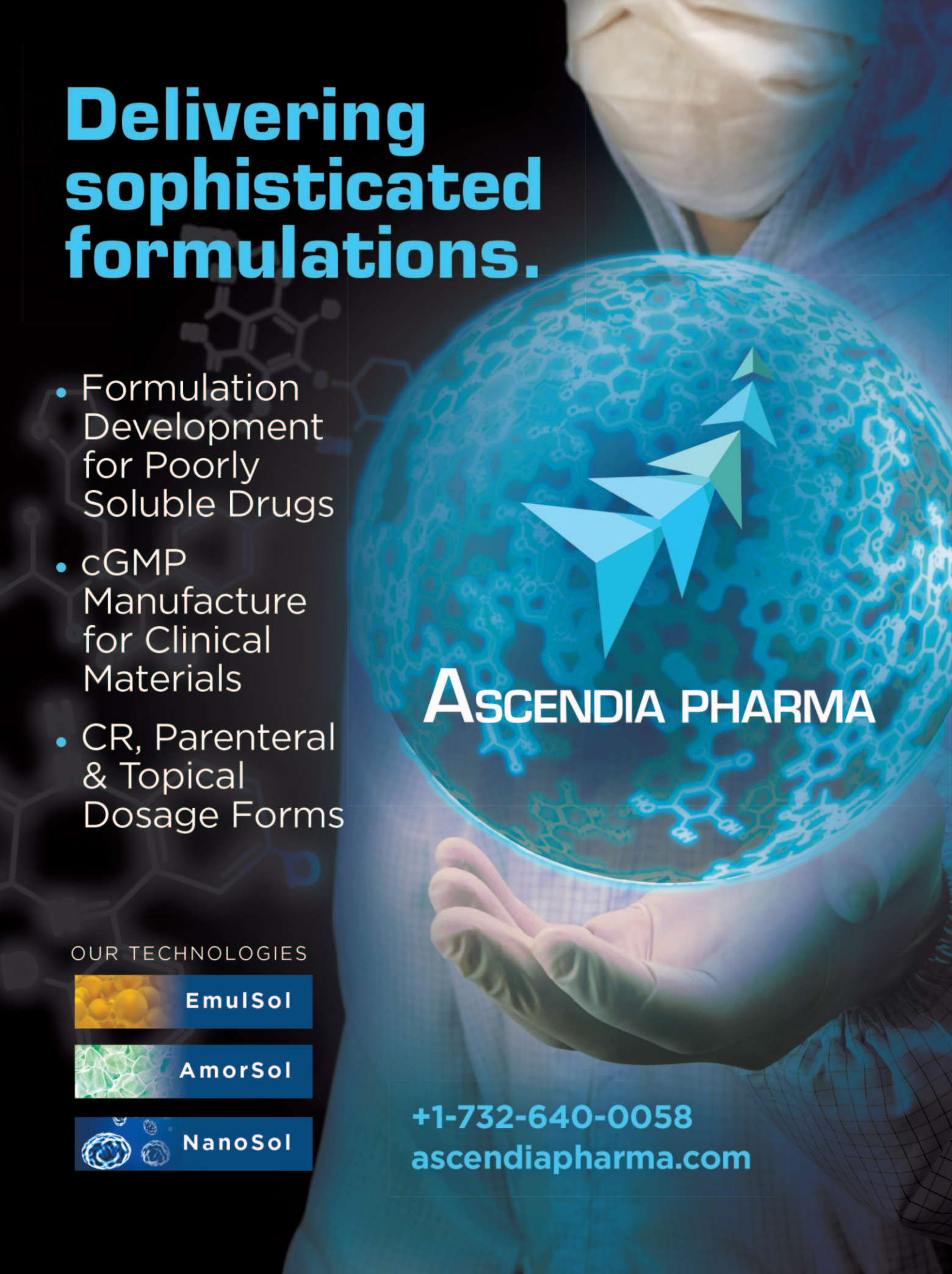
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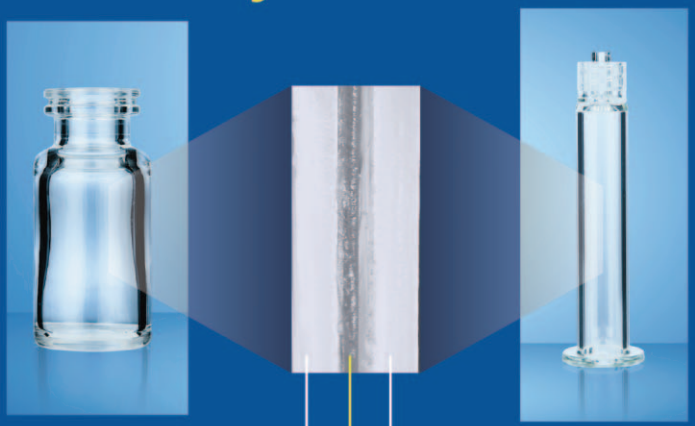

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Drug Development & Delivery

January/February 2022 Vol 22 No 1

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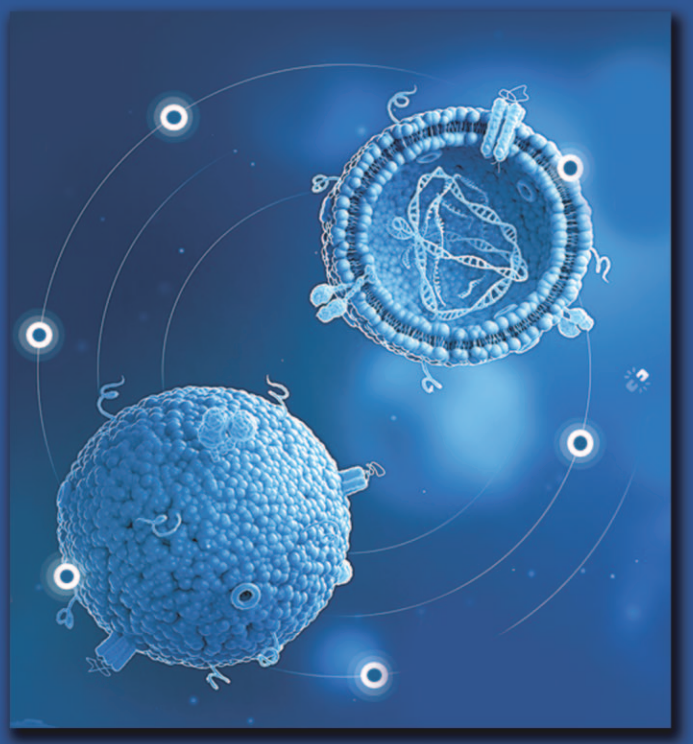
The Promise of Exosomes

"The next frontier in biotechnology is to push beyond the cell membrane and develop therapeutics that target directly inside the cell. The therapeutic opportunities are both obvious and compelling. If we can understand how to safely and reliably target specific cell types, move past the cell membrane, and introduce a critical missing protein — or a set of critical missing proteins — into the cell, we have the potential for a platform that can address many types of diseases and conditions, from diabetes to monogenic diseases, such as cystic fibrosis or Duchenne muscular dystrophy and beyond."

p.28



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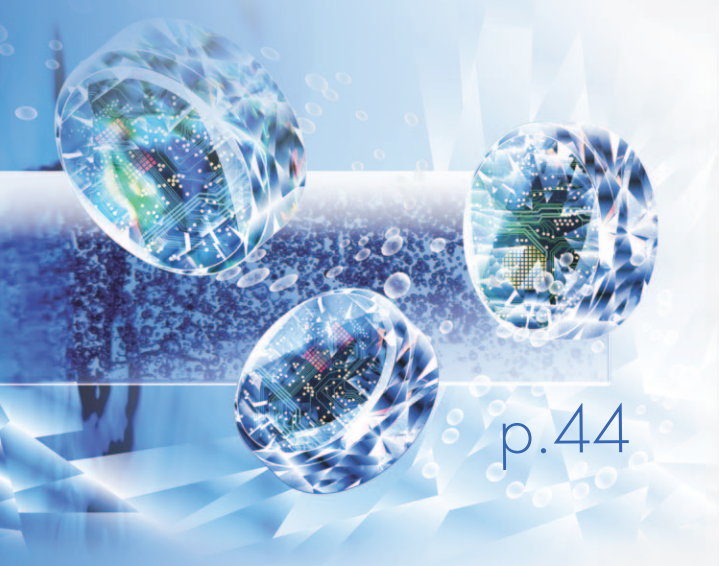
Analytical Testing Trends

"An increasing number of clinical trial registrations, more R&D investment, growing demand for biopharma products, a continued focus on safety and quality, and more third-party testers entering the market are key reasons why the US pharmaceutical analytical testing outsourcing market is expected to reach $5.55 billion in the next 5 years. Globally, the market could reach $12.4 billion by 2028."



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NeoCura & PhoreMost Announce Research Collaboration to Explore Novel Cancer Therapeutics

NeoCura Bio-Medical Technology Co., Ltd. and PhoreMost Limited recently announced an oncology drug discovery research collaboration. As part of the collaboration, PhoreMost's SITESEEKER phenotypic screening platform and NeoCura's full-process RNA drug design platform will be used to investigate the cellular delivery and efficacy of encoded targeted peptides. In this way, the research aims to inform and advance the research and development of innovative anti-cancer therapies.

PhoreMost's SITESEEKER platform can identify the best new therapeutic targets for any chosen disease setting, and rapidly identify how to develop novel drugs to these targets. This has the potential to significantly increase the diversity of novel treatments for cancer and other unmet diseases. Based on proprietary protein interference, or PROTEINi, technology, PhoreMost uses SITESEEKER to probe the entire proteome in a live cell environment for novel druggable targets linked to any chosen disease. This enables the systematic discovery of functionally active peptides which are directly linked to useful therapeutic applications. NeoCura has world-class RNA technology, which can significantly increase the expression efficiency of RNA cargo and improve its in vivo delivery to target tissues.

Dr. Wang Yi, Founder and CEO of NeoCura, said "NeoCura is pleased to establish a collaborative partnership with PhoreMost. We are deeply impressed by PhoreMost's excellent protein interference technology platform and unique target mining capabilities. It is believed that with the leading RNA drug research and development capability of NeoCura and cutting-edge SITESEEKER technology of PhoreMost, more therapeutic potential will be released in the field of research and development of RNA drugs, and the translational process of anti-cancer drugs will be greatly accelerated. Meanwhile, NeoCura also hopes to join hands with more industry leaders in the vigorous development of biomedicine in China."

Dr. Chris Torrance, CEO, PhoreMost, added "This partnership demonstrates the versatility of PhoreMost's SITESEEKER platform, and the range of innovative drug discovery programs it can work within. NeoCura's platform complements PhoreMost's capabilities to unmask cryptic druggable sites across the entire human proteome. RNA delivery of novel therapeutics represents an exciting opportunity for PhoreMost as we aim to significantly increase the diversity and affordability of novel therapeutics for cancer and other unmet diseases."

NeoCura, a R&D based China biotech featuring AI-empowered RNA precision medicine. Founded in 2017, NeoCura is committed to building a global leading RNA innovative drug research and development enterprise. NeoCura brings together the world's top scientists, senior industry experts and first-class academic consultants in AI bioinformatics, tumor immunity, new vaccine research and development, drug delivery, nucleic acid carriers and other areas.

PhoreMost has developed a next-generation phenotypic screening platform called SITESEEKER that can discern the best new targets for future therapy and crucially, how to drug them, which has the potential to significantly increase the diversity and affordability of novel therapeutics for cancer and other unmet diseases.

4D Molecular Therapeutics Announces FDA Fast Track Designation Granted to 4D-125 for the Treatment of X-linked Retinitis Pigmentosa

4D Molecular Therapeutics recently announced the US FDA has granted Fast Track Designation for 4D-125 for treatment of patients with inherited retinal dystrophies due to defects in the RPGR gene, including X-linked Retinitis Pigmentosa (XLRP). 4D-125 is a targeted and evolved R100-based product candidate, which was invented at 4DMT for efficient intravitreal delivery, and is designed to deliver a functional copy of the RPGR gene to photoreceptors in the retina.

"Patients living with XLRP currently have no approved treatments, and they suffer from progressive vision loss and blindness that reduces their quality of life and independence," said Robert Kim, MD, Senior Vice President and Ophthalmology Therapeutic Area Head of 4DMT. "Fast Track Designation is a landmark event for the program and underscores the potential of 4D-125 to address a significant unmet need for those living with XLRP."

The FDA's Fast Track process is designed to accelerate the development and review of treatments for serious and life-threatening diseases where no treatment exists or where the treatment in discovery may provide advantages over what is currently available. A drug candidate that receives Fast Track designation is eligible for more frequent communication with the FDA throughout the drug development process and a rolling and/or priority review of its marketing application if relevant criteria are met.

4D-125 is 4DMT's targeted and evolved R100-based product candidate for XLRP and is designed to deliver a functional copy of the RPGR gene to photoreceptors in the retina. 4DMT is currently enrolling patients in an on-going Phase 1/2 clinical trial. The study employed a standard 3+3 dose-escalation design, followed by dose expansion. In dose-escalation, patients were enrolled in one of two dose cohorts: 3E11 vg/eye and 1E12 vg/eye. The dose expansion phase of the study is enrolling patients at the 1E12 vg/eye dose. The primary objectives of this trial are to evaluate the safety and maximum tolerated dose of 4D-125. Secondary endpoints include assessments of clinical activity, including both visual function and anatomical endpoints.

XLRP is a rare inherited X-linked recessive genetic disorder that causes progressive vision loss and blindness in boys and young men. There are currently no approved therapies for XLRP. Seventy percent of cases are caused by mutations in the retinitis pigmentosa GTPase regulator (RPGR) gene. The estimated worldwide prevalence of XLRP due to RPGR variants is approximately one in 25,600 people, which represents approximately 24,000 patients in the US, and France, Germany, Italy, Spain and the UK (together, EU-5). It is characterized by dysfunction and degeneration of photoreceptors in the retina. Symptoms of XLRP are initially characterized by night blindness, followed by loss of peripheral visual field, decreasing visual acuity and eventually blindness.

4DMT is a clinical-stage company harnessing the power of directed evolution for targeted gene therapies. 4DMT seeks to unlock the full potential of gene therapy using its platform, Therapeutic Vector Evolution, which combines the power of directed evolution with approximately one billion synthetic capsid sequences to invent evolved vectors for use in targeted gene therapy products.

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Malvern Panalytical Expands Pharmaceutical Drug Development Solutions Through Acquisition of Creoptix

Malvern Panalytical recently announced its acquisition of Creoptix AG, a specialist bioanalysis sensor company. The acquisition forms a critical part of Malvern Panalytical's strategy to expand its capabilities in support of drug discovery.

Creoptix provides cutting edge tools for molecular interaction analysis. Engineered around their proprietary Grating-Coupled Interferometry (GCI) technology, these tools enable researchers to access high-quality binding affinity and kinetics data across a broader range of samples than traditional SPR-based solutions, accelerating the discovery and development of new drug substances.

"We are really excited to be bringing the Creoptix team into the Malvern Panalytical family", stated Mark Fleiner, President of Malvern Panalytical. "We have always been driven by our desire to support our customers in the development of ground-breaking new drug products. Creoptix significantly builds on the instrumentation and services capabilities we have to achieve this, strengthening our position in supporting small molecule pharmaceutical development while also significantly growing our capabilities in the fast-growing biopharmaceutical space."

Engineered around their proprietary Grating-Coupled Interferometry (GCI) technology, these tools enable researchers to access high-quality binding affinity and kinetics data across a broader range of samples than traditional SPR-based solutions, accelerating the discovery and development of new drug substances.

Line Stigen Raquet, CEO Creoptix, also sees significant opportunities resulting from joining the Malvern Panalytical team. "The purpose of Creoptix has always been to enable life scientists to accelerate drug discovery", said Line. "Our WAVE portfolio is designed with the vision to advance breakthrough science, and to help scientists develop new and better drugs, faster. We believe that this merger is an exciting opportunity to further accelerate and deliver on our purpose, as we benefit from the exceptional knowledge and global customer reach provided by Malvern Panalytical."

Integration of Creoptix into the Malvern Panalytical family will start in January 2022 and is planned to be completed within the first half of 2022.

We draw on the power of our analytical instruments and services to make the invisible visible and the impossible possible. Through the chemical, physical and structural analysis of materials, our high-precision analytical systems and top-notch services support our customers in creating a better world, helping them to improve everything from the energies that power us and the materials we build with, to the medicines that cure us and the foods we enjoy. We partner with many of the world's biggest companies, universities and research organizations. They value us not only for the power of our solutions, but also for the depth of our expertise, collaboration and integrity. With over 2200 employees, we serve the world, and we are part of Spectris plc, the world-leading precision measurement group. For more information, visit www.malvernpanalytical.com.

Creoptix is a company headquartered in Wädenswil, near Zurich, Switzerland, with a US office in the Boston area. Creoptix was founded in 2009 and has successfully gone through several financing rounds with Eduard Brunner from Start Angels Network, Privilège Ventures and Swisscanto (CH) Private Equity Switzerland Growth I Fund, respectively, as lead investors. Creoptix focuses on next-generation bioanalytical instruments for drug discovery and life sciences for both industry and academic research. Based on its proprietary sensor and microfluidics technology, the Creoptix WAVEsystem provides exceptionally high sensitivity and resolution to study real-time biological interactions involving small molecules, peptides, membrane proteins, biologics, and other molecules even in biofluids like undiluted serum or plasma.

Starton Therapeutics Receives Clinical Trial Authorization in Europe to Initiate Phase 1 Clinical Trial of STAR-LLD Continuous Delivery Lenalidomide

Starton Therapeutics Inc. recently announced it has received a Clinical Trial Authorization (CTA) in the Netherlands to initiate a Phase 1 study evaluating STAR-LLD bioavailability in human subjects.

"This study provides comparative rapid confirmation of blood levels so we can move in to the clinic in multiple myeloma. We have designed the most efficient study to meet regulatory requirements, assess safety, and bring STAR-LLD to a patient population as soon as possible," said Jamie Oliver, Chief Medical Officer.

Pedro Lichtinger, Chairman and Chief Executive Officer, emphasizes "This CTA authorization is an important milestone for Starton, as our first clinical regulatory authorization for the STAR-LLD program."

The Phase 1 study will evaluate the 24-hour bioavailability, safety, tolerability, and pharmacokinetics STAR-LLD in healthy human subjects compared to oral lenalidomide. The Phase 1 portion of the study is an open-label, crossover design used to confirm the plasma concentrations of STAR-LLD versus oral lenalidomide that will be further evaluated in a randomized Phase 1b study in patients with multiple myeloma. STAR-LLD uses an ambulatory continuous subcutaneous infusion pump to deliver Starton's proprietary solubilized lenalidomide. Starton's previous in vivo studies found a 77% reduction in plasma lenalidomide exposure using a continuous subcutaneous infusion versus pulsatile dosing at the daily oral equivalent.

Starton plans to submit additional regulatory applications in other countries as part of its development approach for STAR-LLD.

STAR-LLD is a continuous delivery lenalidomide in development to expand the standard of care for the most common blood cancers, multiple myeloma and chronic lymphocytic leukemia (CLL). A preclinical proof-of-concept study for STAR-LLD demonstrated that MM tumors caused by human myeloma cells grew 25-fold if untreated, five-fold when treated with oral lenalidomide and shrank by 80% with STAR-LLD. The study also showed 100% efficacy (overall response rate ORR) at 144 mcg continuous LLD and 20% tumor elimination vs. 0% ORR with active control with daily pulsatile once daily dosing. STAR-LLD SC is expected to enter clinical studies in Q1 2022. Starton has completed a pre-IND meeting for STAR-LLD SC and all IND-enabling studies. Starton expects to reference prior findings of nonclinical safety for key sections of the New Drug Application (NDA) for REVLIMID(r).

A clinical-stage biotechnology company focused on transforming standard of care therapies with proprietary dermal technology, so people with cancer can receive continuous treatment to live better, longer. Starton's proprietary transdermal technology is intended to increase efficacy of approved drugs, to make them more tolerable and expand their potential use.To learn more, visit www.startontx.com.

Catalent Increases Specialized Packaging Capabilities at its Philadelphia Facility to Support Growing Biologic & Cell & Gene Therapy Markets

Catalent recently announced it has increased cold chain packaging capabilities at its Philadelphia facility to support increased demand for the distribution of biologic drugs, and advanced cell and gene therapies.

Work has been undertaken at the facility to expand the packaging area by around 20,000 square feet and includes the addition of seven new temperature-controlled processing suites, which can operate at either refrigerated or frozen conditions to precisely match the needs of the drugs being handled. Further ambient space has also been added for packaging operations and materials storage.

The new suites include full serialization capabilities, specifically designed for small-scale batches of commercial products. Validation of the equipment is expected to be completed by the end of Q1 2022.

"Advanced therapeutics require increasingly complex handling requirements, and the investment we have made in Philadelphia allows Catalent to operate efficient packaging processes and operations, bridging the gap between clinical scale and niche commercial volumes," commented Ann McMahon, General Manager of Commercial & Integrated Development Operations at Catalent Clinical Supply Services. "The specifically designed packaging areas not only provide optimal commercial opportunities for drug developers, but also the safest working conditions for employees in terms of air exchange rates, carbon dioxide monitoring, and ultraviolet air sanitization."

The 200,000-sq-ft Philadelphia facility is the largest site in Catalent's global clinical supply network and the company's North American Center of Excellence for clinical supply packaging. It includes an on-site pharmacy to support FlexDirect direct-to-patient services for clinical trials, as well as access to Catalent's FastChain demand-led supply services, primary and secondary packaging capabilities, a range of temperature options for storage and distribution, and clinical returns and destruction services.

Catalent is the global leader in enabling pharma, biotech, and consumer health partners to optimize product development, launch, and full life-cycle supply for patients around the world.

With broad and deep scale and expertise in development sciences, delivery technologies, and multi-modality manufacturing, Catalent is a preferred industry partner for personalized medicines, consumer health brand extensions, and blockbuster drugs. Catalent helps accelerate over 1,000 partner programs and launch over 150 new products every year. Its flexible manufacturing platforms at over 50 global sites supply over 70 billion doses of more than 7,000 products to over 1,000 customers annually.

Catalent's expert workforce exceeds 18,000, including more than 2,500 scientists and technicians. Headquartered in Somerset, NJ, the company generated $4 billion in revenue in its 2021 fiscal year. For more information, visit www.catalent.com.

Definitive Agreement to Acquire Exelead Will Strengthen the CDMO Offering for mRNA of the Life Science Business of Merck KGaA, Darmstadt, Germany

Merck KGaA, Darmstadt, Germany recently announced the signing of a definitive agreement to acquire Exelead, a biopharmaceutical contract development and manufacturing organization (CDMO), for approximately $780 million in cash. Exelead specializes in complex injectable formulations, including Lipid Nanoparticle (LNP) based drug delivery technology which is key in mRNA therapeutics for use in Covid-19 and many other indications.

"Novel modalities, particularly mRNA, present a highly attractive business opportunity as pharma and biotech pipelines are increasingly building on them beyond Covid-19. The acquisition of Exelead will further enable us to capture the significant potential of the fast-growing market for mRNA therapies by providing leading CDMO services to our customers," explained Belén Garijo, Chair of the Executive Board and CEO of Merck KGaA, Darmstadt, Germany.

"Exelead's capabilities and expertise will strengthen our CDMO mRNA offering. We are excited to work with Exelead's experienced team. Together, we will provide our customers a unique and truly integrated offering across the mRNA manufacturing process. This will significantly decrease supply chain complexity and enhance speed-to-market to ultimately accelerate access to life-enhancing therapeutics for patients worldwide," added Matthias Heinzel, Member of the Executive Board of Merck KGaA, Darmstadt, Germany and CEO Life Science.

"With the Life Science business sector's long-established expertise, in the biopharmaceutical industry, Exelead will now be in a greater position to serve the needs of customers and patients. The business combination will further strengthen our renowned technological know-how and unique expertise that we bring to the CDMO space," said John Rigg, Chief Executive Officer of Exelead.The acquisition of Exelead is another milestone to accelerate innovation in the Process Solutions business unit of Merck KGaA, Darmstadt, Germany, one of the company's three growth engines ("Big 3"), through targeted smaller to medium-sized acquisitions with high impact. It follows the company's acquisition of AmpTec, a leading Hamburg, Germany-based, mRNA CDMO, that was announced at the beginning of 2021.

The transaction enhances the company's more than 20 years' experience in producing lipids, one of the critical components for the formulation of mRNA therapeutics including Covid-19 vaccines as well as its mRNA manufacturing capabilities. Exelead has more than ten years of experience in all development phases from pre-clinical development to commercial contract manufacturing for LNP formulations, including fill and finish.

Exelead is headquartered in Indianapolis, IN, where it operates its production and employs more than 200 experts. Merck KGaA, Darmstadt, Germany, intends to continue to invest in mRNA as a modality and will scale up this technology at Exelead's existing site in Indianapolis.The transaction is expected to close in the first quarter of 2022 and is subject to regulatory clearances as well as the satisfaction of other customary closing conditions.

BioNTech & Crescendo Biologics Announce Global Collaboration to Develop Multi-Specific Precision Immunotherapies

BioNTech SE and Crescendo Biologics Ltd. recently announced they have entered a multi-target discovery collaboration to develop novel immunotherapies for the treatment of patients with cancer and other diseases. The initial term of the discovery collaboration is three years.

Crescendo will contribute its unique, proprietary, transgenic platform to deliver fully human heavy-chain antibody domains (Humabody VH) against targets nominated by BioNTech. Humabodies represent a novel class of therapeutics that retain the high-affinity binding and specificity of conventional therapeutic antibodies while providing additional advantages such as small size, enhanced tissue and tumor penetration, stability and molecular simplicity due to the lack of a light chain. In particular, the modular nature of Humabodies make them ideally suited for the development of multi-target immunotherapies.

"Crescendo's platform provides excellent properties for exploiting novel targets and target combinations which we believe has great potential for the development of multi-specific mRNA and engineered cell-based therapies in a variety of disease areas," said Ugur Sahin, M.D., Chief Executive Officer and Co-Founder of BioNTech. "We are excited to begin working with Crescendo to further strengthen and expand our multimodal immunotherapy portfolio and deliver breakthrough precision medicines for patients."

"To collaborate with BioNTech and their world-class team is a transformational opportunity for Crescendo. We are looking forward to further leveraging our clinically validated Humabody VH platform within mRNA therapeutics to develop better treatment options for patients," said Theodora Harold, Chief Executive Officer at Crescendo Biologics.

Under the terms of the agreement, Crescendo will receive $40 million upfront, including a cash payment and an equity investment from BioNTech, as well as research funding for the period of the collaboration. BioNTech will be responsible for global development and hold exclusive worldwide commercialization rights on any products arising from the collaboration. Crescendo will be eligible to receive development, regulatory and commercial milestones up to a total of more than $750 million, in addition to tiered royalties on global net sales.

Biopharmaceutical New Technologies is a next generation immunotherapy company pioneering novel therapies for cancer and other serious diseases. The Company exploits a wide array of computational discovery and therapeutic drug platforms for the rapid development of novel biopharmaceuticals. Its broad portfolio of oncology product candidates includes individualized and off-the-shelf mRNA-based therapies, innovative chimeric antigen receptor T cells, bi-specific checkpoint immuno-modulators, targeted cancer antibodies and small molecules.

Crescendo Biologics is a private, clinical stage immuno-oncology company developing novel, targeted T cell enhancing Humabody therapeutics. Leading its proprietary pipeline, Crescendo Biologics has developed CB307, a novel half-life extended CD137 x PSMA Humabody for the selective activation of tumour-specific T cells exclusively within the tumour microenvironment. CB307 is designed to achieve a longer lasting anti-cancer effect whilst avoiding systemic toxicity, and the clinical programme for CB307 is underway in patients with PSMA positive solid tumors. The company's ability to develop multi-functional Humabody therapeutics is based on its unique, patent protected, transgenic mouse platform generating fully human VH domain building blocks (Humabody VH).

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Emerald Health Pharmaceuticals Receives IND Clearance to Begin Phase 2 Clinical Trial of EHP-101 for Relapsing Forms of Multiple Sclerosis

Emerald Health Pharmaceuticals Inc. has received clearance of its Investigational New Drug (IND) application by the U.S. Food and Drug Administration (FDA) to begin enrolling patients in its Phase 2a clinical trial of EHP-101 for certain relapsing forms of multiple sclerosis (RMS), specifically relapsing-remitting MS (RRMS) and active secondary progressive MS (SPMS).

"The absence of therapeutic options that go beyond treating symptoms, inflammation and reducing the incidence of relapses represents a significant unmet need for multiple sclerosis patients," said Dr. Jim DeMesa, Chief Executive Officer. "Our preclinical studies of EHP-101 demonstrated a promising effect on disease progression by preventing demyelination of the neurons, the major issue associated with MS, but also by stimulating their remyelination or regeneration of new myelin, in several multiple sclerosis animal models. We look forward to assessing some of the early indicators of activity of EHP-101 in this Phase 2a study of patients suffering from relapsing forms of MS, the most common disease course."

The international Phase 2a, open-label, multicenter dose-finding study in patients with RMS will evaluate the safety, tolerability, and preliminary efficacy of the Company's lead product candidate, EHP-101. The study is designed to enroll 50 patients who suffer from RMS in approximately 30 study centers in the US, the EU, and Australia. Patients will receive escalating doses administered once or twice daily and will be evaluated over a treatment duration of 24 weeks.

Along with assessments of safety and tolerability, efficacy endpoints in the Phase 2a MS study will include changes from baseline in brain lesion activity as measured by magnetic resonance imaging (MRI), disease progression and disability status, proportion of relapse-free patients, patient-reported outcomes, and assessments of biomarkers such as changes in neurofilament light chain levels in the blood, which is a well-known diagnostic, prognostic and disease monitoring biomarker for neurological diseases.

The relapsing forms of multiple sclerosis include RRMS, SPMS and CIS. Relapsing remitting multiple sclerosis (RRMS) is defined by periodic neurologic symptoms caused by inflammatory attacks on myelin (the layers of insulating membranes surrounding nerve fibers in the central nervous system) as well as on nerve fibers themselves. During these inflammatory attacks, activated immune cells cause small, localized areas of damage (called demyelination) which produce the symptoms of MS. Approximately 85% of people with MS are initially diagnosed with RRMS.

Secondary progressive MS (SPMS) follows an initial relapsing-remitting course. Most people who are diagnosed with RRMS will eventually transition to a secondary progressive course in which there is a progressive worsening of neurologic function (accumulation of disability) over time. SPMS can be further characterized as either active (with relapses and/or evidence of new MRI activity during a specified period of time) or not active, as well as with progression (evidence of disability accrual over time, with or without relapses or new MRI activity) or without progression.

Clinical isolated syndrome (CIS) is a first episode of neurologic symptoms of MS. When CIS is accompanied by lesions on a brain MRI there is a high likelihood of a second episode and diagnosis of RRMS.

SK Inc., the Second Largest Conglomerate in South Korea, Has Invested $350 Million in the Center for Breakthrough Medicines

The Center for Breakthrough Medicines recently announced it has received $350 million in equity financing from SK Inc.. CBM is partnering with SK to create the world's largest end-to-end cell and gene therapy contract development and manufacturing organization (CDMO).

CBM will leverage this investment to enhance its fully integrated pre-clinical through commercial manufacturing capabilities with world class automation and infrastructure. Existing and future capabilities include process development, viral vector manufacturing, cell processing, plasmid DNA, cell banking, and a full suite of complimentary analytical development and testing capabilities.

"We chose to partner with SK based on our shared deep desire to cure cancer and eradicate genetic disease," said Brian O'Neill, Chairman, Center for Breakthrough Medicines. "Thousands of people are dying every day, and we have the ability to cure patients by manufacturing these new technologies. This unprecedented collaboration will allow us to bring over 700,000 square feet of capacity online, and hire 2,000 of the world's most brilliant, advanced therapy experts, all at the Discovery Labs site in King of Prussia, Pennsylvania."

"SK is the perfect strategic partner to enable CBM's core mission of expediting approval for cell and gene therapies," added Audrey Greenberg, Co-Founder, Center for Breakthrough Medicines. "SK's mission of delivering value and happiness for all, their emphasis on a culture of safety and quality, and their global reach creates an ideal match for CBM allowing us to scale and deliver in an unprecedented manner."

In addition to supporting lab and GMP suite build-out, this investment will also enable strategic joint ventures, sponsored research agreements, and development of proprietary technology platforms.

"People of all ages are suffering from cancer and genetic diseases around the world. Our partnership with SK accelerates our ability to bring together the world's most brilliant minds to develop and manufacture cures," said Joerg Ahlgrimm, President and CEO, Center for Breakthrough Medicines. "The partnership with SK, Inc. allows us to more fully realize our mission to save lives by accelerating the development and manufacturing of advanced therapies. This mission is the foundation of our company culture – we always put our partners and patients first, it is the premise of CBM and why we come to work every day."

"CBM's strong management team and geographic location in Philadelphia, the birthplace of the cell & gene therapy industry, were core elements in our desire to invest in the company," said Mr. Dong Hoon Lee, Executive Vice President of SK Inc.,
"Through our investment in CBM, which was made through SK Pharmteco, an SK holding company, we have secured a crucial foundation for realizing SK pharmteco's vison in 2025 to become a global top-tier CDMO."

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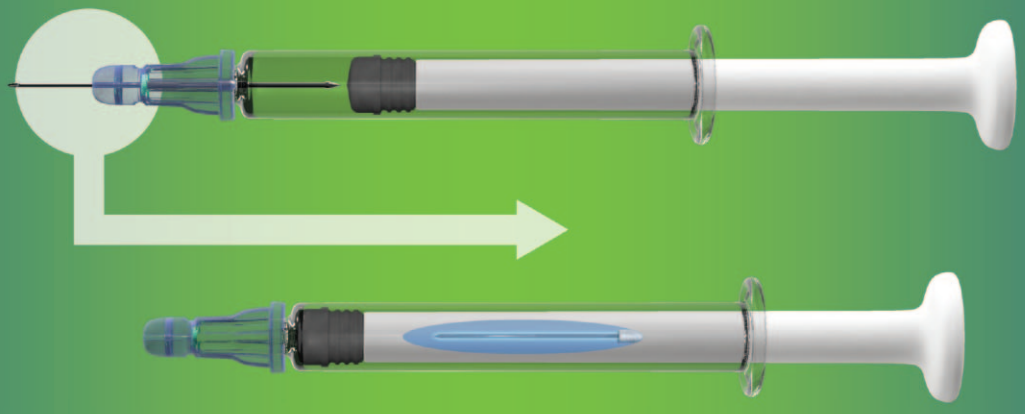

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CREDENCE MEDSYSTEMS

FORMULATION FORUM

Formulation & Process of Lipid Nanoparticles for Delivery of Small Molecules & Biologicals

By: Jim Huang, PhD, Founder & CEO, Ascendia Pharmaceuticals

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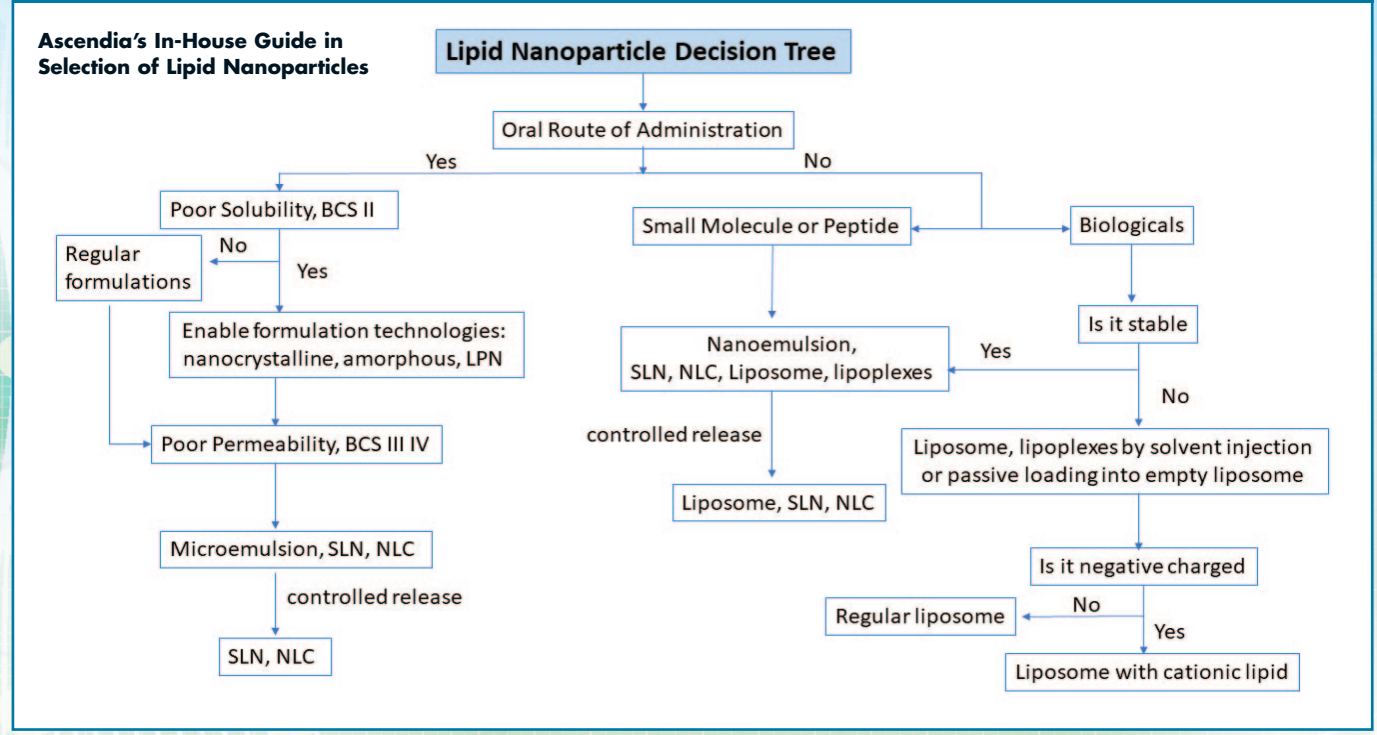
INTRODUCTION

Lipid nanoparticles (LNPs) are nano-sized particles that are mainly composed of lipids. Traditionally, LNPs are referred to as liposomes, lipoplexes, solid lipid nanoparticles, nanostructured lipid nanoparticles, microemulsions, and nanoemulsions, which are mainly used in the delivery of small molecules and peptides. Recently, lipid nanoparticles have emerged as a drug delivery system for biologicals, especially for the COVID-19 mRNA vaccines in which LNPs play a vital role in transporting mRNA into the target cells.

Due to the lipid material's unique properties and excellent biocompatibility, LNPs are suitable for use in nanomedicines, vaccines, nutrition supplements, and diagnosis by different routes of administration, such as oral, topical, pulmonary, and parenteral injection. Figure 1 shows a general guide and practice in the selection of lipid nanoparticles for different types of therapeutic moiety by Ascendia Pharma.

FIGURE 1



LIQUID-FORM LIPID NANOPARTICLES

Microemulsions and nano-emulsions are a form of liquid-form lipid nanoparticles that are mainly composed of lipids in liquid forms, which typically are composed of a lipid carrier, co-solvent, surfactants, and co-surfactant. Depending on the surfactant level, it can be classified as a (1) microemulsion (thermodynamic stable lipid concentrate with high level of surfactant); or (2) nano-emulsion, which is a pre-formed nano-system as a result of high-energy inputs and is kinetically stable in the aqueous phase.

Microemulsions

For oral route of administration, lipid nanoparticles can be frequently presented as a lipid concentrate (microemulsion); upon oral administration, the lipid concentrate will be diluted by GI fluid and spontaneously form lipid nanoparticles. Due to lipophilicity of the lipidic material, oral lipid nanoparticles have traditionally been used to enhance solubility and bioavailability of small molecule compounds and peptides that have solubility and cell permeability issues (namely BCS II and IV compounds). Lipid nanoparticle-based drug delivery systems enhance the oral bioavailability of drugs via three main mechanisms: (1) increasing dissolution and solubility by pre-dissolving drugs in lipid carriers; (2) increasing drug permeability in the GI tract by inhibition of P-gp and other efflux transporters; and (3) bypassing the first-pass metabolism of the drug through the lymphatic absorption processes. In addition, lipid-based drug delivery systems have the potential to decrease the food-effect and to increase reproducibility of the pharmacokinetic profile of those orally administered drugs by reducing erratic absorption.

Lipid concentrate can be characterized into the following five categories. The two most popular systems used for insoluble drugs are Type II/IIIA: Self-Emulsifying Drug Delivery Systems (SEDDS) and Type IIIB: Self-Microemulsifying Drug Delivery Systems (SMEDDS), forming microemulsions that are thermodynamically stable.

Lipid concentrate for oral formulations can be processed simply by mixing, dissolving, and filling into bottles or liquid-filled capsules. Hard gelatin/HPMC capsules, which offer flexibility for use from the early to commercial stages of development and different options for trade dress, are frequently chosen for lipid-based oral formulations.

Nano-emulsions

Nano-emulsions, which are composed of nano-sized droplets dispersed in a continuous phase, can be classified into either oil-in-water (O/W) or water-in-oil (W/O). Oil-in-water emulsions have gained significant application in the drug delivery of lipophilic drugs or nutritional supplements by parenteral, oral, and topical routes of administration, whereas W/O emulsions have increased their application for delivery of hydrophilic small molecules and biologicals.

As a result of small droplet size as low as <50 nm, the large surface area, and a reduction in surface tension, nano-sized emulsions can provide unique solutions for overcoming drug solubility, permeability, and stability problems. Compared to microemulsions, nano-emulsions contain much less of the surfactants, and as such, are meta-stable and more susceptible to Ostwald ripening. In addition, nano-emulsions require greater kinetic formation energy, and are usually prepared using high-pressure homogenization, microfluidics, or ultrasonic generators. However, a well-formulated nano-emulsion will maintain its physical-chemical stability through its shelf-life of at least 2 to 5 years. Because of the undesirable side-effects caused by many solvents and surfactants (in fact, the FDA places daily intake limits on such ingredients), microemulsions are disadvantageous compared to nano-emulsions for human use via the parenteral route. In addition, nano-emulsions possess benefits in reduction of injection pain and thrombophlebitis, enabling of targeted drug delivery, and reduction of drug toxicity.

A few lipid-based nano-emulsion pharmaceutical products have been marketed in the past years, such as Intralipid Infusion as a parenteral supplement formulated as 10%-30% Soybean Oil, 1.2% Egg Yolk Phospholipids, 1.7% Glycerin, and Water for Injection; and Propofol Emulsion Injection formulated in a lipid emulsion containing 10% soybean oil, 2.25% glycerol, and 1.2% egg lecithin. Nano-emulsions have also been proven safe for use as a vaccine adjuvant, eg, Humenza®, an Influenza H1N1 vaccine from Sanofi Pasteur, which is composed of an O/W type emulsion AF03; and the MF59 adjuvanted subunit influenza vaccine (Fluad), which was approved for those aged 65 years and older. MF59 is Novartis' proprietary O/W emulsion consisting of 4.3% (vol/vol) squalene, 0.5% Tween 80, and 0.5% Span 85, in citrate buffer (10 mM). MF59 was prepared via homogenization, sterilized by a 0.22-µm pore size filter.

SOLID LIPID NANOPARTICLES & STRUCTURE LIPID NANOPARTICLES

Solid lipid nanoparticles (SLNs) were developed as an alternative system to the existing emulsions dosage forms in which the liquid lipid (ie, oil) was replaced by a solid lipid. SLNs not only offer the benefits of emulsion in excellent biocompatibility, high bioavailability,

"LPNs are a very versatile formulation technology that can be applied to drug delivery of a variety of small/large molecules, peptides, and biologicals. Due to lipids' unique properties and excellent biocompatibility, LNPs are suitable for use in pharmaceuticals, nanomedicines, vaccines, nutritional supplements, and diagnosis by different routes of administration, such as oral, topical, pulmonary, and parenteral injection."

nano-sized and large surface area, but could also maintain high drug loading and sustained delivery of drug from its matrix.

Structure lipid nanoparticles (NLCs) were introduced by adding a small quantity of liquid lipid to the solid lipid for the purpose to overcome the potential issues with SLNs in potential reduction in drug loading due to drug expulsion by crystallization or transformation of the solid lipid over the storage period. NLCs could increase drug loading by combining solid lipids with small amounts of liquid lipids or by the formation of an amorphous type NLC by introduction of special lipids, such as hydroxyl stearate and isopropyl myristate to the solid lipid.

Like traditional emulsion formulation, SLNs/NLCs are made up of solid lipid and/or liquid lipid, emulsifier, and water. The lipids used may be triglycerides, partial glycerides, fatty acids, cholesterol, and waxes.

Process for SLN/NLC

Similar to the emulsion process, high-shear, high-pressure homogenization can be utilized for SLNs/NLCs. Normally, homogenization is carried out at temperatures above the melting point of the lipid to form a lower size and a better uniform droplet size distribution. In some cases, cold homogenization can be performed to maintain solid state of lipid and to avoid segregation of drug and lipid due to drug migration to the lipid surface during the homogenization process.

LIPOSOMES & LIPOPLEXES

Discovered in the 1960s, liposomes consist of one or several lipid bilayers, ranging in size from 20 nm and ~1000 nm; the unique structure of which enables loading of both hydrophilic drugs into its aqueous interior and hydrophobic drugs in its lipid bilayer. Liposomes can also be classified into two categories: multilamellar vesicles (MLVs) vs unilamellar vesicles. Unilamellar vesicles can further be divided into large unilamellar vesicles (LUVs) and small unilamellar vesicles (SUVs). The surface charges of LNPs can be positive or negative, mainly determined by the lipid head groups. Absolute zeta potentials of over 30 mV should be a good indicator of stable LPN. Lipoplexes are electrostatic complexes formed by mixing preformed cationic lipid liposomes with an anionic therapeutic moiety (such as siRNA) an aqueous environment.

Unilamellar liposomes can alter their PK and biodistribution profile of therapeutic entities and thus enhance therapeutic efficacy and reduce toxicity of drugs. Successful liposomal products in the market include: 1) Doxil® for treatment of ovarian cancer, Depocyt®, Amphotec®, DaunoXome®, MyocetV, etc for small molecule delivery; 2) Epaxal® (HAV adsorbed to the surface of special liposomes, virosomes) and Inflexal® for vaccines; 3) Onpattro® for siRNA, Comirnaty® (Pfizer COVID-19 Vaccine), and Moderna COVID-19 vaccine for mRNA. Multivesicular liposomal products include Depocyt®, DepoDurT™ and Exparel® by DepoFoamT™ technology. The multivesicular liposomes in the 3- to 30-µm size range can release drug over an extended of time ranging from 1 to 30 days.

Liposomes for small molecule delivery are most commonly made up from phospholipids, such as phosphatidylcholines (PC), phosphatidylethanolamines (PE), phosphatidylserines (PS), phosphatidylglycerols (PG), and helper lipids, such as cholesterol and PEG-Lipid. For example, bupivacaine liposome injectable suspension (Brand Name: Exparel) contains bupivacaine at a nominal concentration of 13.3 mg/mL. Inactive ingredients and their nominal concentrations are: cholesterol, 4.7 mg/mL; 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), 0.9 mg/mL; tricaprylin, 2.0 mg/mL; and 1, 2-dierucoylphosphatidylcholine (DEPC), 8.2

mg/mL. The pH of Exparel is in the range of 5.8 to 7.4. In liposomal formulation design, attention should be given to the phase transition temperature of liposomes in relation to liposome formation and stability. During manufacturing, above the temperature, phospholipids exist in liquid crystalline phase that helps hydrophobic tails of phospholipids oriented to form closely continuous bilayer membrane, whereas below the temperature, phospholipids exist in a gel state and are not able to form liposomes. In addition, the effect of formulation on liposome stability, storage temperature, and drug release is also related to the phase transition temperature; drug release from the liposome is accelerated at a temperature above the phase transition temperature.

Typically, RNA liposomes consist of cationic lipids and DSPC as the main ingredients together with the helper lipids, such as cholesterol and PEG-lipid. Helper lipids help stabilize the physical stability, enhance circulation time in blood, and improve RNA delivery by promoting destabilization of the lipid bilayer. In some cases, Lipoplexes that formed by mixing preformed cationic lipid liposomes with anionic siRNA in an aqueous environment can be used. For RNA liposomal delivery, due to negative charge of RNA, cationic lipids or ionizable cationic lipids become the critical ingredients to improve RNA encapsulation efficiency. Furthermore, cationic lipid can reduce RNA degradation in neutral body fluid because of complexation between RNA and cationic lipids and to promote endosomal escape inside the cell. Ionizable cationic lipids are a newer class of lipids that is characterized by their ability to change their charge as a function of pH. At a low pH, they are protonated and carry a positive charge; at neutral pH, they are neutral without charge. The positive charge at a low pH help encapsule RNA with good efficiency, whereas the neutral charge of the LPN in the physiology pH help reduce the exposure of RNA to the body fluid that minimize RNA degradation. When LPN is at the target cell, the low pH environment helps enhance LPN cellular uptake due to interaction of cationic lipid with negative change cell membrane that breaks down the bio-layer membrane and helps RNA in endosomal escape and release into the target cell organ.

For example, the compositions of the lipid nanoparticles of the current Pfizer/BioNtech/Moderna vaccine have very similar composition. Both contain an ionizable lipid, PEGylated lipid, phospholipid distearoylphosphatidylcholine (DSPC), and cholesterol. Those nanoparticles are 80 to100 nm in diameter. For example, Each 0.3-mL dose of the Pfizer-BioNTech COVID-19 Vaccine supplied in multiple dose vials includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose.

Liposome Preparation Methods

There are several ways to make liposomes. The most popular methods are film hydration and the solvent injection method. The film hydration method involves drying down lipids from organic solvent, rehydrating the lipids in aqueous media, formation of liposome by a process, loading the liposomes by active or passive method (may not necessary if drug is co-processed with lipid), purification of liposomes by ultrafiltration method, sterile filtration, lyophilization if necessary, and fill and finish into a vial. The solvent injection method begins the process by initially mixing the lipid ethanol solution with an aqueous solution at a certain ratio/speed and then following steps afterward similar to the film hydration method.

The key step for liposome preparation is the formation of liposomes after initial mixing. This step may involve high pressure, high shear mixing (homogenizer and microfluidizer), extrusion, microfluidic chip mixing, sonication, freeze thaw, etc. This step will determine the particle size distribution of liposomes, drug loading, liposome structure, and drug distribution in the liposome.

SUMMARY

LPNs are a very versatile formulation technology that can be applied to drug delivery of a variety of small/large molecules, peptides, and biologicals. Due to lipid's unique properties and excellent biocompatibility, LNPs are suitable for use in pharmaceuticals, nanomedicines, vaccines, nutritional supplements, and diagnosis by different routes of administration, such as oral, topical, pulmonary, and parenteral injection. ◆

ORGAN-ON-A-CHIP

A Novel Way to Accurately Test Delivery of Non-Standard Formulations

By: David Hughes, PhD

INTRODUCTION

In 2019, the immediate study of lung biology and respiratory viruses became a global priority with the advent of the COVID-19 pandemic. There was considerable pressure on academic researchers and the pharmaceutical industry to fast-track therapies to treat the critically ill, develop vaccines to control the spread of disease, and understand the basic biology of this devastating new virus.

Typically, it had taken 10-15 years to develop a vaccine before the pandemic, yet the pressure of a global crisis delivered multiple safe and efficacious COVID-19 vaccines within just 1 year. Consequently, the industry is now more receptive to innovative ways of shortening and improving the efficiency of the drug discovery process. Currently, only 1 in 10 drugs in clinical trials is ultimately approved for therapeutic use – the other 9 fail due to a lack of efficacy or safety concerns. One reason for such high drug failure rates is the limited ability of preclinical tests to predict human responses. More than a decade ago, a push toward incorporating more physiologically relevant *in vitro* assays into the drug discovery workflow began to address this.

CHALLENGES ASSOCIATED WITH LUNG MODELS

The task of recreating a lung in the lab, however, is a fundamentally difficult one. Lungs are multi-cellular, with complex architecture. They provide the interface between the outside environment and our blood, and the process of breathing puts them under continuous mechanical stimulation. Dosing is also a challenge. Viruses, drugs, and chemicals arrive in our lungs as aerosols, so how do we accurately characterize and recreate this process? The predictive power of even the most sophisticated lung model will diminish if it is not dosed in a physiologically relevant manner.

Traditional models of the lung range from simple immortalized cells in culture, through complex *in vitro* models, like organoids, to an array of small and large animals. The most recent model type to enter the field is Organ-on-a-Chip (OOC). Here, primary human cells and tissues are cultured under physiologically relevant conditions to recapitulate an organ's *in vivo* phenotype and function. Before OOC, a primary human bronchial epithelial cell model was the most physiologically relevant model available. Cells cultured at an air-liquid interface for 14 days up to 3 months could produce mucus and beating cilia.[1] However, since 2010, when the Wyss Institute developed the first lung-on-a-chip model, the pace of lung-on-a-chip development has been rapid.[2] These complex *in vitro* models now offer a wealth of new possibilities over and above traditional approaches for modelling disease, profiling drug ADME, and predicting toxicity.

LUNG-ON-A-CHIP TECHNOLOGY

To recreate the complex air-liquid histoarchitecture of the lung, most lung-on-a-chip models feature epithelial and endothelial compartments separated by a porous membrane. Cell culture medium is usually fed to the endothelial side, playing the role of blood, whereas the epithelial compartment remains open to the air to simulate the *in vivo* airway. Lung epithelial cells represent the foundations of the model; however, additional cell types can be added (eg, endothelial cells to mimic vasculature, fibroblasts, smooth muscle cells, tissue-resident,

and circulating immune cells) to recreate the function and phenotype of the lung more accurately. These cells may come from healthy donors or those with lung disease. As a final layer of sophistication, fluid shear created by flowing the cell culture medium and mechanical stretching provide cells with biochemical and mechanical signaling cues similar to those experienced in the body.[2]

Like all models, different lung-on-a-chip systems have their pros, cons, and limitations. Before selecting one, it is important to ensure a fit versus context of use. Two configurations of lung-on-a-chip have emerged: the microfluidic "chip" and the insert-based system. Each presents its opportunities and challenges.

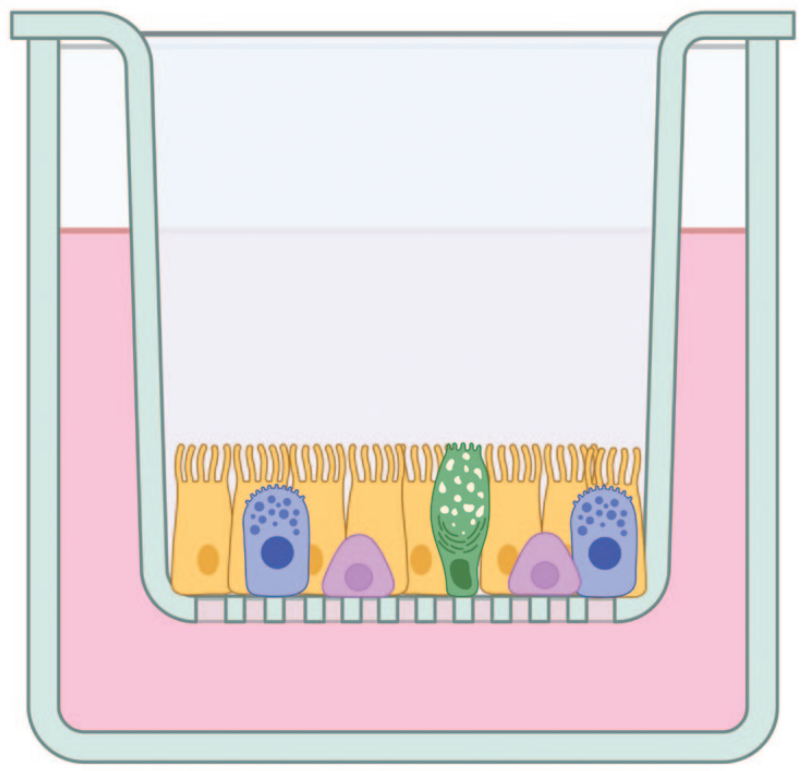
LUNG-ON-A-CHIP: THE MICROFLUIDIC "CHIP" SYSTEM

As exemplified by Huh *et al*, microfluidic "chip" solutions require cell seeding into a pair of microfluidic channels separated by a porous membrane.[2] The porous membrane is formed from an elastomeric material which, when stretched, provides mechanical stimulation. Upper and lower channels hold lung epithelial and endothelial cells, respectively. In some instances, cell culture medium flows through the lower channel to mimic blood flow. The cells in each channel form polarized monolayers that enable the transport of species across the barrier to be studied. An advantage of this configuration is that the application of mechanical stimulation enhances lung phenotype over non-stimulated controls, whilst the limited thickness of the "chip" makes it well suited to analysis via *in situ* imaging.[2] However, there are also drawbacks to this approach. Set-up is relatively complex, which limits the number of "chips" that can be run simultaneously and therefore throughput is low. Further, in encapsulated microfluidic devices, it is challenging to seed cells at the beginning of an experiment and collect cells at the end, requiring experience, specialist training, and a steady hand. Moreover, these configurations are not easily interfaceable with lab automation or aerosol dosing platforms, and valid concerns surround the extent of drug absorption into the polydimethylsiloxane (PDMS) elastomeric "chips".

LUNG-ON-A-CHIP: THE INSERT-BASED SYSTEM

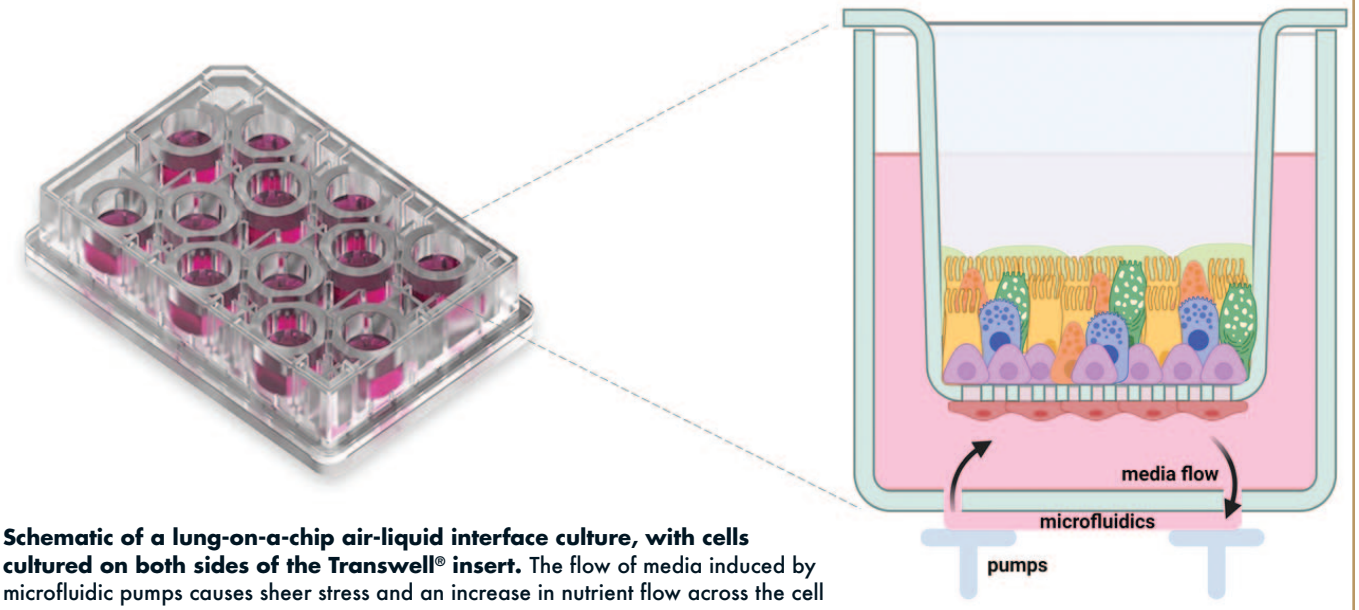
Insert-based lung-on-a-chip systems take a different approach, building upon standardized and scalable industry-proven technology through the introduction of fluid flow. These models utilize cell culture inserts with a porous membrane base (eg, Transwells®) that have been widely used for barrier model studies (such as gut, lung, and skin) under static conditions for decades. In these systems, lung epithelial cells are seeded into the upper apical compartment at the air-liquid interface, with the option to add endothelial cells into the lower basolateral compartment. By adding flow to one or both compartments, it is possible to recreate shear forces that

FIGURE 1



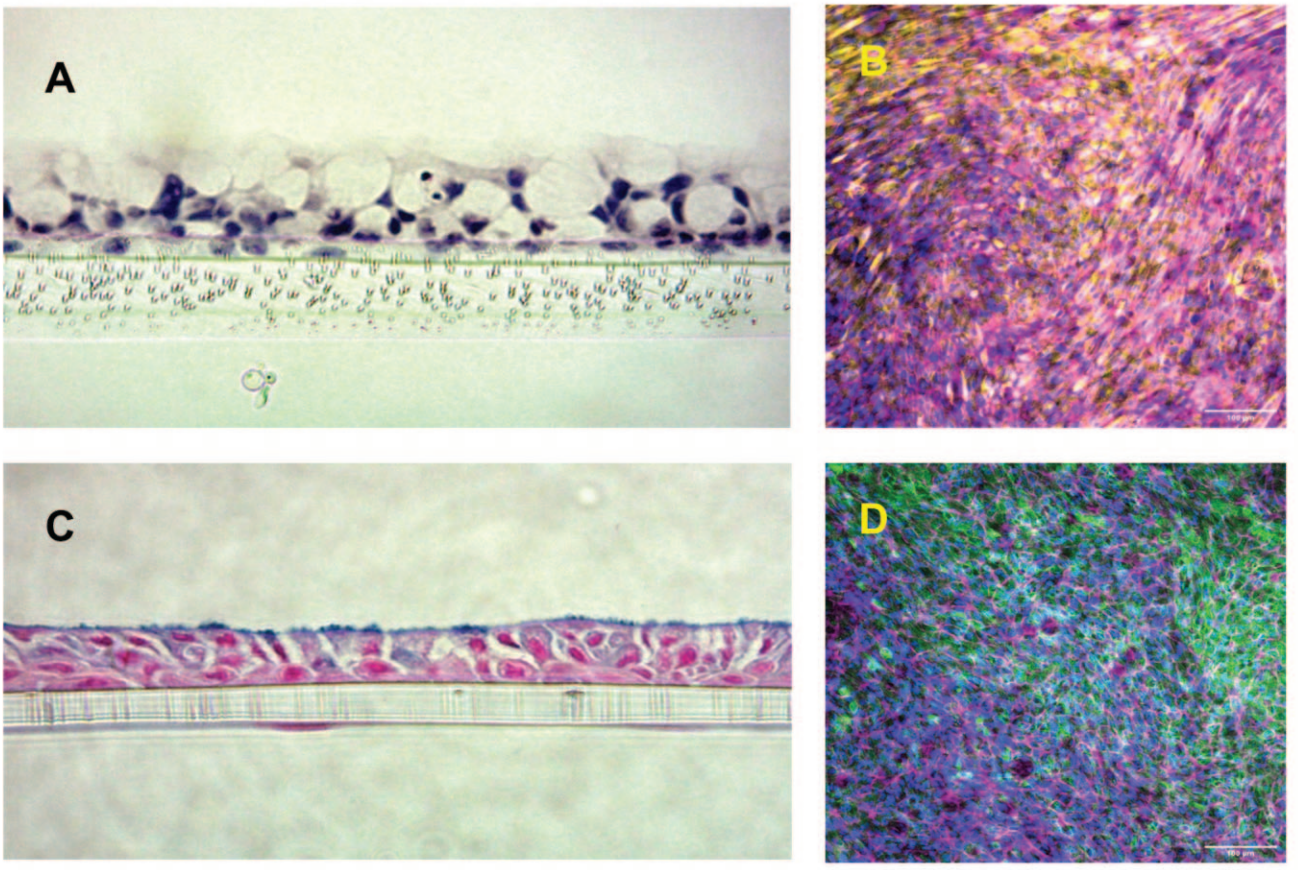
Schematic of traditional air-liquid interface culture on Transwell® insert, under static conditions.

FIGURE 2



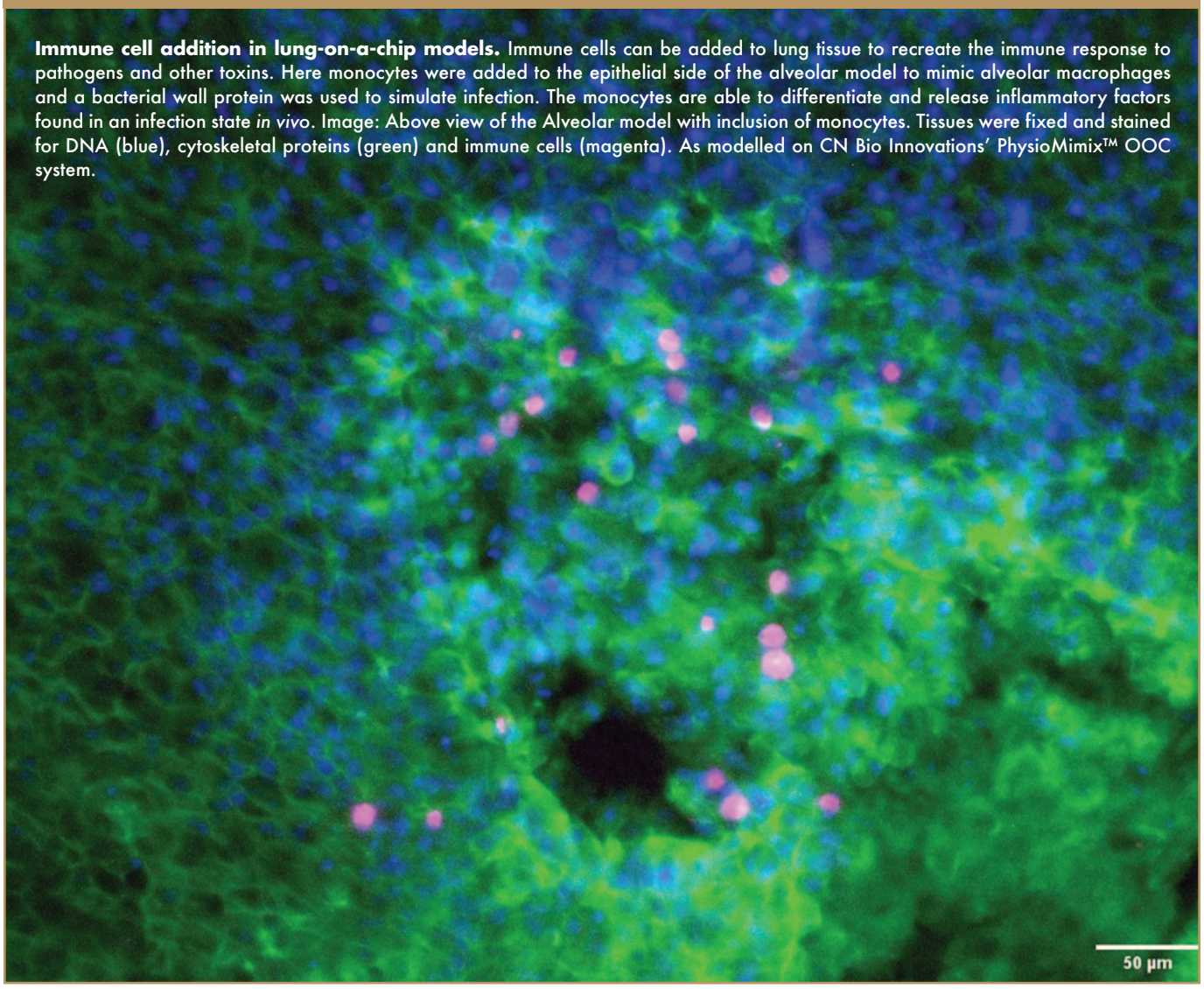
Schematic of a lung-on-a-chip air-liquid interface culture, with cells cultured on both sides of the Transwell® insert. The flow of media induced by microfluidic pumps causes sheer stress and an increase in nutrient flow across the cell layer. This induces a more physiological tissue phenotype.

FIGURE 3



Alveolar and bronchiolar models. (A) Cross-section of an Alveolar model which displays alveolar sac-like structures and a multi-layered epithelium. Tissue was fixed before sectioning and staining with H&E. **(B)** An above view of the Alveolar model. Tissues were fixed and stained for DNA (blue), cytoskeletal proteins (magenta) and an alveolar cell marker (yellow). **(C)** Cross-section of the Bronchiolar model showing a pseudostratified epithelium. Tissue was fixed before sectioning and staining with Alcian Blue. **(D)** An above view of the Bronchiolar model. Tissues were fixed and stained for DNA (blue), cytoskeletal proteins (magenta) and mucus (green). As modelled on CN Bio Innovations' PhysioMimix™ OOC system.

FIGURE 4



Immune cell addition in lung-on-a-chip models. Immune cells can be added to lung tissue to recreate the immune response to pathogens and other toxins. Here monocytes were added to the epithelial side of the alveolar model to mimic alveolar macrophages and a bacterial wall protein was used to simulate infection. The monocytes are able to differentiate and release inflammatory factors found in an infection state *in vivo*. Image: Above view of the Alveolar model with inclusion of monocytes. Tissues were fixed and stained for DNA (blue), cytoskeletal proteins (green) and immune cells (magenta). As modelled on CN Bio Innovations' PhysioMimix™ OOC system.

analogously stimulate cells to mechanical stimulation. Lung tissues that closely match the *in vivo* phenotype are also created, but unlike "chips", inserts can easily be accessed (for example for washing to avoid mucus build-up or examining barrier integrity) and removed for use in commercial aerosol testing systems. Inserts do not absorb drugs; access for imaging is easy; and they offer a plentiful supply of cells/culture medium for comprehensive biochemical analyses.

MULTI-ORGAN OOC MODELS

Additionally, organs within the human body do not operate in isolation; they operate as a system. Multi-organ OOC models offer the potential to perform systemic interaction and organ-to-organ crosstalk studies (such as ADME), which previously required animal studies. Whereas animal studies have the disadvantage of inter-species differences generating misleading results, OOC can offer human-relevant insights for better decision-making. Organs grown *in vitro* on "chips" can be made to work in these powerful multi-organ OOC models, but the insert-based approach is much more amenable to linking organs, and therefore also promotes the end goal of a complete human body-on-a-chip.[3]

Figures 1 and 2 show primary human lung epithelial and endothelial cells co-cultured in standard static conditions and in a commercially available lung-on-a-chip insert-based model, respectively, to create bronchial and alveolar airway models. By exposing standard Transwell inserts to fluid flow, the system recapitulates the differing tissue architecture, cell populations, and barrier functions of both lung sections. In bronchial models, fluid flow induces a

mucus-producing ciliated pseudostratified epithelium with polarized and aligned endothelium.

In alveolar models, fluid flow uniquely stimulates alveolar type I and II cells to produce alveolar sac-like structures not observable in traditional static culture or other lung-on-a-chip models (Figure 3). ACE2 receptor expression and the potential to include immune cells in both the apical and basal side of the system means these models are compatible with SARS-CoV-2 infection and immune response studies (Figure 4).

Lung-on-a-chip systems, therefore, can recapitulate significant aspects of human lung physiology and pathology, but it is important not to compromise the predictive value of these models by dosing drugs, viruses, and other species in a non-physiologically relevant manner. Applying samples in a solution may be simple but is far from the *in vivo* situation. To deliver representative vapors, aerosols, smoke, dry powders, and microorganism-containing droplets into lung-on-a-chip systems requires them to be integrated with well-characterized dosing apparatus. This can be achieved through device adaptation, ie, by modifying the output of the apparatus to direct into either the channels of a microfluidic chip system or the apical compartment of an insert system. A simpler approach involves removing inserts and installing them into standard dosing apparatus.[4] By combining phenotypically relevant lung models with industry-proven dosing apparatus and dosimetry, the translatability of data derived from short-term exposure and permeability studies should improve.

FUTURE OUTLOOK FOR ORGAN-ON-A-CHIP

Ultimately, the goal of OOC technology is to improve the translatability of data between the lab and the clinic. Through a lung-on-a-chip approach, it is possible to recreate the histoarchitecture, phenotype, and function of bronchial and alveolar areas of the lung. Different lung-on-a-chip configurations provide researchers with the opportunity to select the right system for their application, context of use, and throughput needs. These advanced *in vitro* tools model diseases like COVID-19, predict the human ADME properties of inhaled drugs, and identify potential toxicants, but to ensure data translatability between the laboratory and the clinic, it is crucial to dose these models with airborne species. Once the predictive power of these models becomes more recognized, their widespread adoption into preclinical drug development workflows has the potential to help deliver therapeutics to patients more rapidly. ◆

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BIOGRAPHY

Dr. David Hughes is CEO of CN Bio Innovations, a leading OOC company that has developed single and multi-organ microphysiological systems that improve the accuracy and efficiency of drug discovery, including the PhysioMimix™ lab-benchtop instruments. He is also Principal Investigator on a $26-million US DARPA contract toward development of human *in vitro* multi-organ platforms and leads a €4-million EU FP7 program aimed at developing stem cell-derived models of human liver. Dr. Hughes graduated from the University of Oxford with a Masters in Engineering Science and Doctorate in Chemical Engineering.

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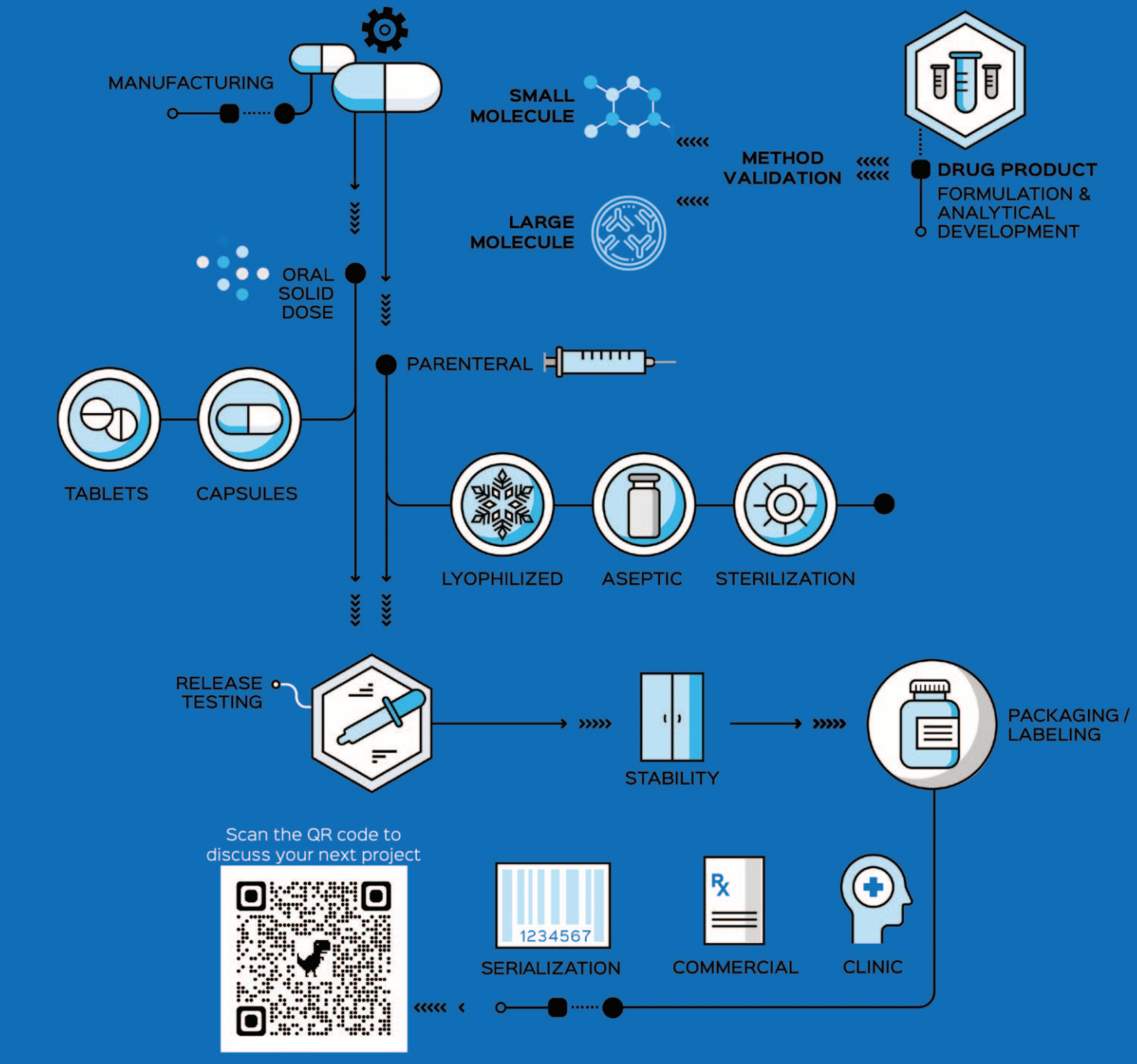

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EXOSOMES

The Next Evolution in Therapy Delivery Beyond the Cell Membrane: The Promise of Exosomes

By: Linda Marbán, PhD

INTRODUCTION

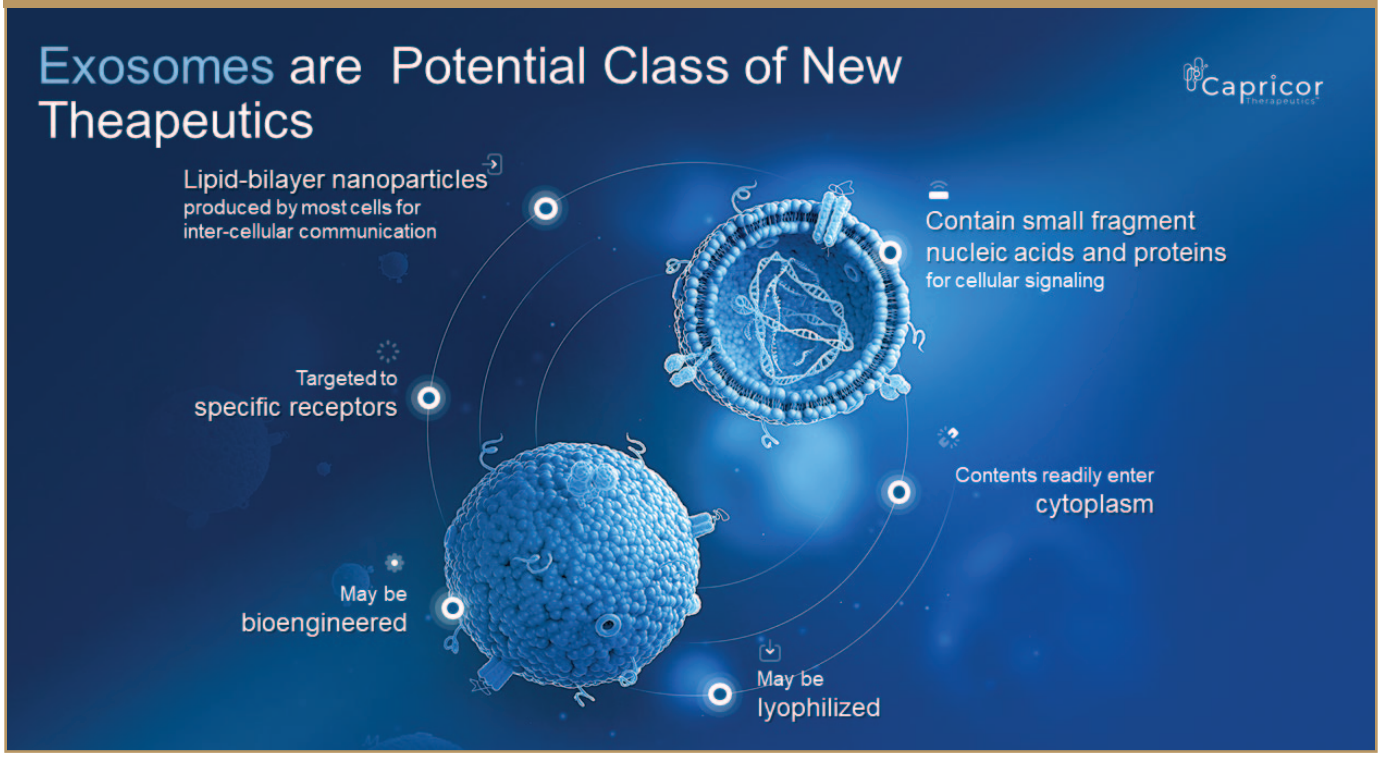
The business of biotechnology has always been the pursuit of new frontiers; what's next is always impossible until the breakthrough that makes it possible.

The challenge is that innovative ideas and applications are often difficult for people to understand. While most medical professionals know the top 10 selling pharmaceuticals today are antibodies, it's easy to forget the earliest recombinant humanized monoclonal IgG1 antibody therapies like Avastin struggled to get approval, because the science surrounding such biologics was so new.

Yet the frontiers in antibodies and other biologic therapeutics that have evolved over the past 3 decades have improved millions of lives for patients with certain types of cancers, to multiple sclerosis, to HIV, arthritis, and anemia associated with chronic renal failure and beyond.

The next frontier in biotechnology is to push beyond the cell membrane and develop therapeutics that target directly inside the cell. The therapeutic opportunities are both obvious and compelling. If we can understand how to safely and reliably target specific cell types, move past the cell membrane, and introduce a critical missing protein — or a set of critical missing proteins — into the cell, we have the potential for a platform that can address many types of diseases and conditions, from diabetes to monogenic diseases, such as cystic fibrosis or Duchenne muscular dystrophy and beyond.

FIGURE 1



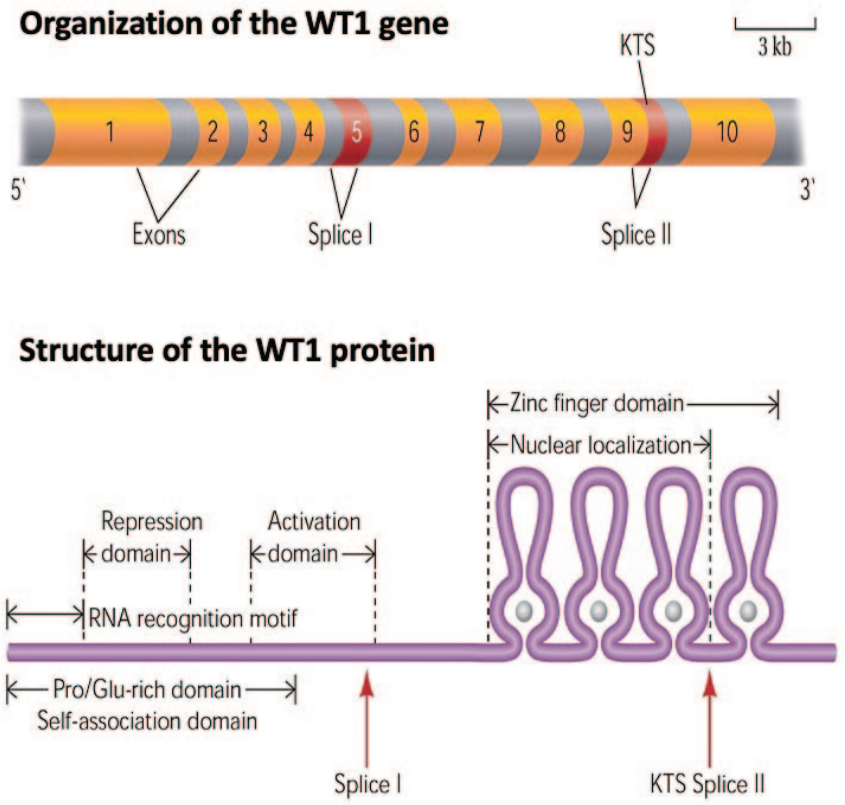
The world has just had a glimpse of this new reality. The recent successes of the mRNA COVID-19 vaccines now being successfully injected into arms across the globe are an important evolutionary step forward in therapy delivery. mRNA medicines are not small molecules, like traditional pharmaceutical drugs, nor are they traditional biologics (such as recombinant proteins and monoclonal antibodies) – which were the origins of the biotech industry. Rather, mRNA medicines are sets of instructions that direct cells in the body to make all the proteins required for life, as well as to prevent or fight disease.

BioNTech/Pfizer's and Moderna's mRNA vaccines both use lipid nanoparticles as mRNA carriers. These vaccines rely on the delivery of mRNA into the cytoplasm of host cells, where it can be transcribed into antigenic proteins to trigger the production of neutralizing antibodies. Therefore, mRNA vaccines require a delivery vehicle that not only protects the nucleic acid from degradation, but allows the mRNA to get into cells.[1]

The answer was to pack the mRNA into protective lipid nanoparticles (LNPs) that would then carry the mRNA into the cells. Once inside the cells, the mRNA instructions teach the cells to make a harmless piece of what is called the "spike protein" found on the surface of the virus that causes COVID-19. Once the protein piece is made, the cell breaks down the instructions and eliminates them.

Next, the antigen presenting cell (APC) displays the protein piece on its surface together with major histocompatibility complex (MHC). Our immune systems recognize that the protein doesn't belong there and begin building an immune response and making antibodies, like what happens in natural infection against COVID-19. By the end of the process, our bodies have learned how to protect against future infection.

FIGURE 2



Organization of the WT1 Gene & Basic Structure of the WT1 Protein

Since a promising delivery system like lipid nanoparticles has been demonstrated to work at scale, why does the world need to keep pushing the frontier?

While the scientific community has recognized the power of RNA as a mediator of disease modification, the conundrum of delivery has haunted the field. While lipid nanoparticles, which have been in development for upward of 30 years, are a good start, they by no means will be the end game in terms of therapeutic development of intracellular drug delivery, and the great frontier of personalized medicine.

The need to continually push the frontier is self-evident: the development of new and better therapies depends entirely on fundamental research. Discovery is a journey that has no end. So, it is fascinating that the problem of delivery of therapeutics could be solved by nature. Perhaps the best way to get past the cell membrane is to deliver contents the same way that cells send information to each other. And that is by the exosome, which in the case of targeted therapy delivery, has been identified as an alternative that shows powerful promise.

WHAT ADVANTAGES COULD EXOSOMES OFFER THAT LIPID NANOPARTICLES DO NOT?

mRNA strands are not only fragile, but they are large and negatively charged. Exosomes are a bigger carrier. mRNA is three to four orders of magnitude larger than molecules that readily diffuse into cells. Second, exosomes can help mitigate

the dense negative charge of mRNA. That charge electrostatically repulses the anionic cell membrane, preventing its uptake. Lastly, unlike lipid nanoparticles, exosomes aren't toxic. The toxicity of lipid nanoparticles isn't a problem for a COVID-19 vaccine that only requires one or two doses. But it's unlikely to be a good strategy for a therapeutic that must be delivered monthly or even more frequently. While there is real work ahead, significant progress has already been made.

WHAT ARE EXOSOMES?

Exosomes are nano-sized, membrane-enclosed vesicles that are secreted by essentially all cells and contain bioactive molecules, including proteins, RNAs, and microRNAs. Exosomes are found in all body fluids including blood, saliva, urine, and breast milk. For example, a patient who receives a blood transfusion safely receives trillions of exosomes.

As Dr. Stephen Gould, PhD, Professor of Biological Chemistry at Johns Hopkins University and Capricor Executive Consultant explains, "Exosomes are the body's natural way of sending complex signals between cells and tissues. As a result, exosome-based vaccines have the potential to elicit more effective immune reactions against infectious agents and cancers, while exosome-based therapeutics have the potential to stabilize drugs and deliver them to their intended site of action."

Initially, scientists believed exosomes were simply a means of cellular waste disposal. However, further analysis, which took almost a decade, showed that the contents of the exosome were not trash but rather were mediators of cellular behavior. To put it plainly, exosomes are the words of cells. They are how cells communicate to each other and give each other the tools to deal with injury or disease.

Later, science discovered that exosomes may aid in disease diagnosis. A liquid biopsy of exosomes can reveal their complex cargo, and a multicomponent analysis may help doctors understand both disease progression and how well the patient is responding to therapy.

The past decade has witnessed a nearly tenfold increase in publications (115 in 2006, 1,010 in 2015). This growing body of studies indicate a functional, targeted, mechanism-driven accumulation of specific cellular components in exosomes, suggesting that they have a role in regulating intercellular communication — particularly at times of injury.[2] Put more colloquially, exosomes can serve as an addressable delivery carrying a "repair toolbox" of proteins, RNAs, and lipids from one cell to another at the moment that cell needs it. What's more, RNA in exosomes is protected from RNase degradation and is stable under various temperature and pH conditions.[3]

An exosome, as a single unit, is far more complicated than any typical signaling molecule and is packed with dozens to hundreds of different proteins and different RNAs. What makes exosomes an attractive therapeutic delivery vehicle or a vaccine template is that concentrations of the molecules on the exosomes don't change relative to one another as they travel away from the point source. This means when one cell wants to send multifactorial signals to other cells doing it via an exosome is far more efficient and effective.

It enables enhanced signaling from a single molecule — rather than the cell interacting with one growth factor, an exosome can deliver signals from dozens or hundreds of individual copies of that one molecule.

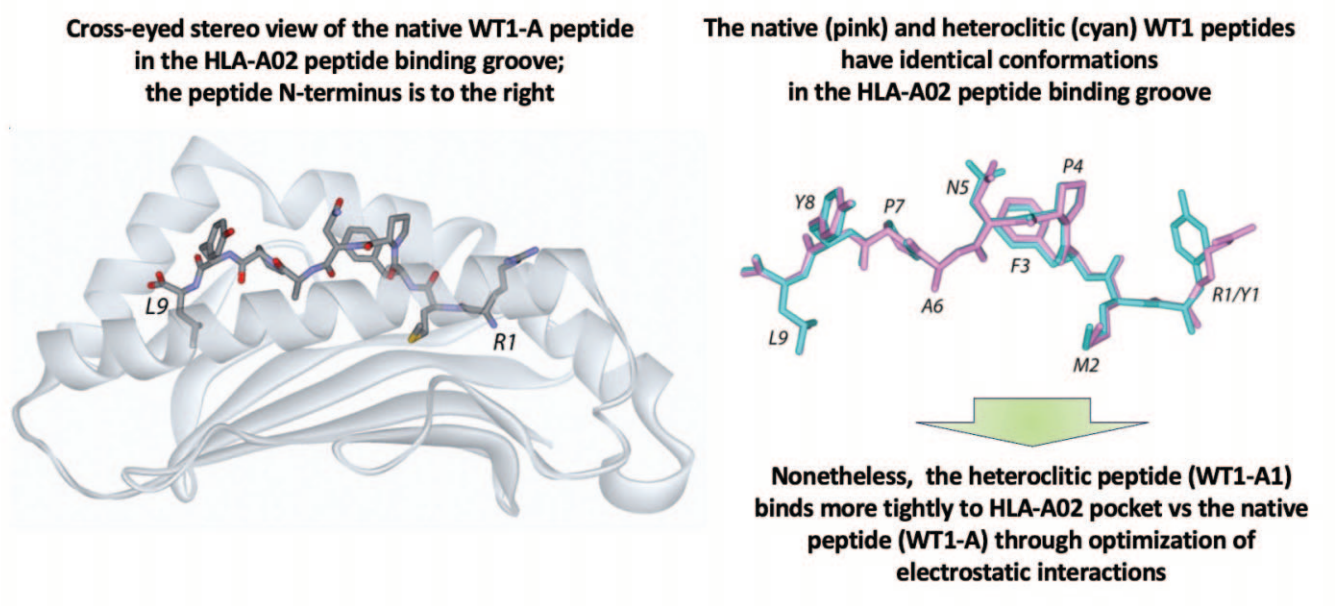
It's also possible to enable multi-dimensional signaling because multiple signaling molecules can be placed on the surface.

Essentially, there are three potential uses for exosomes as pharmaceutical agents. First, they can be collected as a sample from a person's blood and used as a biomarker of potential pathogenesis. One very important use of exosomes in this way is to determine if cancer is ready to or has metastasized. Measurement of internal contents of the exosome can sometimes predict cancer progression before any other way is measurable. There is an entire field developing around exosome diagnostics.

Another way to use exosomes is to harness the endogenous healing power of a specific cell type. For instance, Capricor has a cell therapy product, CAP-1002, which has known immunomodulatory and regenerative properties. It has been shown that the mechanism of action of the cells are via release of exosomes from the infused cells that travel to sites of injury and stimulate anti-inflammatory and healing pathways. Many companies are pursuing this angle as it allows the benefits of cell therapy without the fragility of using living cells.

Finally, perhaps the best way to use exosomes is as nature's delivery system. Throughout this review, we have discussed the power and potential of the exosome as a delivery system for RNA's, proteins, and even lipids (fats). This is the most complicated way to use exosomes, but the path that has the greatest potential benefit. Custom loaded exosomes can lead to biological impact that is designed specifi-

FIGURE 3



Overview of the WT1-A (RMF...)/HLA-A02 & WT1-A1 (YMF...)/HLA-A02 pMHC Class I Complexes

cally. It essentially becomes a magic bullet of therapy, delivering the contents inside the cell, which can lead to a variety of translational and post-translational modifications, the ramifications of which are relatively long lasting and targeted.

Exosomes act as messengers to regulate the functions of neighboring cells. Preclinical research has shown that exogenously administered exosomes can direct or, in some cases, re-direct cellular activity, thereby supporting their therapeutic potential. Their size, ease of crossing cell membranes, and ability to communicate in native cellular language makes them an exciting, emerging class of potential therapeutic agents.

Further, it is believed that a selective packaging mechanism is involved in the loading of exosomes, but such a mechanism has not yet been demonstrated. It has been suggested that it may be based, in part, on RNA "zip codes," that are used by the cell to actively place RNAs in their proper positions in the cell, but this has not yet been proven.[4]

WHAT WOULD MAKE AN IDEAL DELIVERY VEHICLE FOR THERAPEUTIC TREATMENTS?

Broadly, an ideal delivery vehicle for therapeutic treatments should follow Hippocrates dictum to "do no harm." More specifically, it should:

- Be specific to the targeting sites with low toxicity to other organs
- Offer high encapsulation and delivery efficiencies
- Protects the payload while in circulation
- Maintain a steady release profile
- Be easy to store, handle, reconstitute, and administer

TABLE 1

Lipid Nanoparticles	Exosomes
Not easily targetable	Exosomes are driven to deliver cargo to specific recipient cells, due to the unique membrane proteins and lipids that can bind to specific receptors at the recipient cells, thus enhancing the delivery efficiency.[1]
Higher immunogenicity	One of the potential advantages of exosomes is that they are are similar in composition to the body's own cells and therefore have lower immunogenicity. For example, Exosomes can cross the blood brain barrier and deliver therapeutic siRNA safely and effectively into the brain with little toxic effects or immunogenicity even after repeated dosage.[2]
Higher toxicity; can accumulate in the spleen and liver tissues instead of disease sites.[3]	Lower toxicity

FIGURE 4

GPS Constituent Peptides: 3-D Structure & Molecular Formulas

Exosomes meet most or all of these criteria quite well.

LIPID NANOPARTICLES VERSUS EXOSOMES

Why use an exosome when lipid nanoparticles (LNP) are easy to make, easy to quality assure and control, and are inexpensive? The answer is that LNPs may not be as safe for repeated delivery. There are known consequences of toxicity of the LNP and furthermore, the immune system may ultimately reject the LNPs in a repeated delivery therapeutic paradigm. Taken together, the need for safe and effective ways to get bioactive molecules inside the cell is highly warranted. Furthermore, engineering of an LNP may not be a cost-effective solution compared to engineering of an exosome. Exosomes are a likely candidate to fill this gap in the development of novel biotherapies.

OTHER ADVANTAGES OF EXOSOMES

Targeting

Exosomes are driven to deliver cargo to specific recipient cells, due to the unique membrane proteins and lipids that can bind to specific receptors at the recipient cells, thus enhancing the delivery efficiency. The most common mechanism for targeted drug delivery is membrane fusion via a ligand-receptor interaction. Exosomes and other extracellular vesicles are thought to interact with the plasma membrane of target cells by rolling, followed by binding of specific vesicle membrane proteins with their cell receptors, fusion to the target plasma membrane, and release of cargo molecules into the cytoplasm.[5]

Low Toxicity to Other Organs

Exosomes have not shown evidence of toxicity to the spleen or liver and do not seem to cause a pathologic immune response.

Ease of Storage & Handling

Because exosomes are a cell-free substance, they can be stored, handled, reconstituted, and administered in a similar fashion to common biopharmaceutical products such as antibodies.

Encapsulation & Delivery

Capricor is developing a precision-engineered exosome platform technology that can carry defined sets of effector molecules that exert their effects through defined mechanisms of action. These have potential for use in vaccine development, vesicle-mediated protein therapies, and treatment of inherited diseases.

Payload Protection

Exosomes are low-immunogenic in nature — the immune system does not attack them because they are similar in composition to the body's own cells.

Release Profile

As methodologies are developed to manufacture exosomes, critical quality attributes will be easy to establish as will quantification of bioactivity. This assures a standard release profile and a well-defined mechanism of action.

WHAT'S NEXT FOR EXOSOMES?

While exosomes hold powerful promise and deserve the scientific and pharmaceutical industry attention they are receiving, there are challenges that remain to be fully overcome:

- As of today, there is limited to no large scale production of exosomes. Large scale production of exosomes will require more efficient and optimized production and purification strategies.
- First in-human clinical trials will define the critical path forward, which will encompass how rigorously regulators want to define quality attributes.
- Loading exosomes with cargo is possible, but that leading to correction of a disease process has yet to be shown

THE FUTURE IS NOW

Harnessing the power of our own bodies has been the goal of biotechnology for decades. The latest frontier is to get across the cell membrane safely to drive protein expression with long lasting effects on function.

First, it was antibody therapy where we can use the immune system to our advantage to treat a wide array of diseases. Now we are looking deeper to fix errors of metabolism or genetic mutations by using the efficient and effective cellular machinery already in our own bodies. The hurdle has been to get beyond the cell membrane, and now, at last, we have that opportunity with the exosome. Exosomes are slated to change the way medicines are developed and diseases are treated. We are excited to participate in that journey and look forward to breaking down the barriers of treating pathologies associated with intracellular errors.

THREE THINGS TO CONSIDER DOING NOW

1. Begin reviewing the available scientific studies and papers. There is a high level of global interest in the subject, and a growing number of resources available.
2. Consider what practical uses exosomes might have for potential therapies in or entering your pipeline.
3. Open conversations with the industry leaders working to advance the state of the art. Share your requirements and concerns, and ask them what they're learning and what's possible today. ◆

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BIOGRAPHY

Dr. Linda Marbán is the Chief Executive Officer of Capricor Therapeutics, a clinical-stage biotech company developing novel cell and exosome-based therapeutics for the treatment of diseases. As co-founder of Capricor, Inc., its wholly-owned subsidiary, she has been with Capricor, Inc. since 2005 and became its Chief Executive Officer in 2010. She combines her background in research with her business experience to lead the company and create a path to commercialization for its novel therapies. Dr. Marbán's deep knowledge of the cardiac space, in particular, allows her to provide unique direction for the company's development and growth. From 2003 to 2009, she was with Excigen, Inc., a biotechnology start-up company, where she was responsible for business development, operations, preclinical research, and supervising the development of gene therapy products in a joint development agreement with Genzyme Corp. Dr. Marbán began her career in academic science, first at the Cleveland Clinic Foundation working on the biophysical properties of cardiac muscle, and continued into to a postdoctoral fellowship at Johns Hopkins University (JHU). She earned her PhD from Case Western Reserve University in Cardiac Physiology.

COATING TECHNOLOGY

Combining a State-of-the-Art Bromobutyl Formulation With a Proven ETFE Film for Exceptional Chemical Performance

By: Julie Suman, PhD, Sebastien Cordier, and Estelle Verger

INTRODUCTION

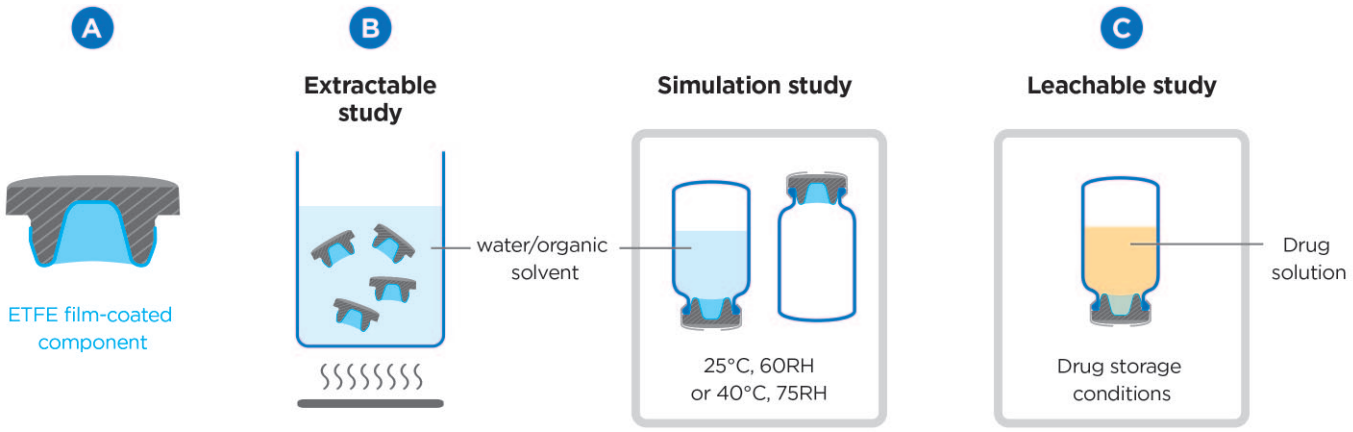
When developing a new drug product, a generic, or repurposing an existing drug, the selection of the right packaging is an essential step. The primary container, which is in direct contact with the drug product, plays a critical role in preserving the drug's integrity from the initial point of production, packaging, distribution, and storage to the moment it is administered. The reliability of the primary container is also essential in ensuring safety for the patient or the healthcare practitioner, which, aside from the human impact, can have significant financial implications for the drug manufacturer if anything does go wrong.

Primary injectable drug packaging is usually composed of two parts: a glass container and a closure component. The latter must ensure the impermeable closure of the container and allow for an easy and safe collection of the drug product. Elastomers are the material of choice for these applications, but they also come with their own set of challenges in terms of integrity and safety. Compared with glass, which is mostly inert, rubber elastomers are the product of petrochemistry, requiring the use of various chemicals for vulcanization, and may therefore threaten the chemical integrity and safety of injectable drugs.

Except in specific cases, such as pre-filled syringes needle shields, and tip caps for which permeable rubbers are used (i.e., polyisoprene, styrene-butadiene), the pharma industry relies mostly on Halobutyls for its water/gas impermeability and especially the low level of chemicals they release, referred to as extractables and leachables (E&L). Over the years, the research and development activities of pharma rubber manufacturers have focused on optimizing Chlorobutyl and Bromobutyl formulations to limit the incidence of E&L while preserving the functional performances of the rubber.

In recent years, the pharma market has seen a significant rise in biologics. These highly complex molecules account for more than 70% of the current pharma market's value, grew at an annual rate of 11% between 2018 and 2020 and are forecasted to grow globally at an annual rate of 9% through 2026.[1,2] Over the past 5 years, four of the top five selling drugs in the US were injectable biologics, and 57% of the pharma pipeline consists of biologics.[1,3] However, if biologics hold great promise for addressing unmet therapeutic needs, they are also highly sensitive, and choosing the right packaging is critical for successful drug development and delivery. In the context of COVID19, where the timely development of a vaccine is crucial, solutions that further minimize the risk of drug/container interaction are essential to ease regulatory approval and accelerate time-to-market.

These concerns can be addressed with coating technologies, which have demonstrated their ability to enhance drug-container compatibility. Ethylene tetrafluoroethylene (ETFE) films are the most common coating technology on the market. In principle, they form a physico-chemical barrier between the elastomer and the drug, helping to prevent the transfer of rubber chemicals into the solution. However, because of the repellant properties of the film and its relative stiffness, it cannot simply be applied all over the elastomer as it would likely tear and would prevent the elas-



Representation of the experimental setup of the various type of studies. A. Representation of the position of the ETFE film on a stopper. B. Extractable study: full immersion of the stopper and analysis of components extracted by the solution. Simulation study: only the coated part is exposed to the inside of the vial for analyzing the soluble and volatile compounds that may be transferred inside the vial when exposed to various model solvents. C. Representation of the leachable study where the elastomer is in contact with the final drug solution.

tomer from making direct contact with the glass to ensure container closure integrity.

To address these challenges, Aptar Pharma has developed PremiumCoat®, a line of vial stoppers and syringe plungers that combine the benefits of ETFE films with the quality of Aptar Pharma's Bromobutyl formulation, proprietary designs, and state-of-the-art processes. The chemical performances of PremiumCoat® are demonstrated through a case study that compared the results of coated components with the results obtained with equivalent uncoated Bromobutyl components. The case study shows that the addition of the ETFE film greatly reduces the number and quantity of compounds that can be leached from the Bromobutyl, demonstrating that the ETFE film acts as a barrier that limits the transfer of E&L into the drug product.

SIMULATION STUDY, A TOOL FOR ASSESSING THE EFFICIENCY OF THE ETFE FILM

The choice of the closure component is crucial, and chemical performance is key to ensure patient safety. To illustrate this point, the early 2000s witnessed pure red blood cell aplasia (PRCA) cases spike after the use of Erythropoietin (EPO). Extractables from the rubber have been identified as a cause of EPO aggregates formation that may have in turn elicited an auto-immune response and caused PRCA.[4,5]

Extractables

The FDA defines extractables as all the organic and inorganic chemical species that can be released from the surfaces of components used in the manufacture and storage of drug products under laboratory conditions. Standard extractable studies are performed by fully submerging the elastomeric component in a solvent (water at different pH, with a range of organic solvents at varying polarities) and forcing the extraction by heating the system (Figure 1B). The extraction solution is then analyzed to identify and quantify the compounds that got extracted. This approach simulates extreme conditions and aims to identify all compounds that may be found in the final drug product. These studies are mandatory for regulatory submission, can be performed by the component supplier or the pharma company, and can help drug developers to better anticipate potential incompatibilities they may face during leachable studies.

Leachables

Leachables are defined as the organic and inorganic chemical species that can be released from the surfaces of components used in the manufacture and storage of drug products under conditions of normal use. Leachable studies, which represent real-life conditions, expose the elastomeric components to the actual drug solution (Figure 1C, which is then analyzed to identify compounds that have been leached from the rubber. These studies are often performed simultaneously with drug stability assays, as requested by regulatory bodies, and inform drug developers of the compounds that may be found in the drug product prior to patient administration.

Simulation Studies

In the case of film-coated elastomers, the film protects the part of the component that is exposed to the drug solution. Extractable studies do not evaluate the action of the film itself, as this requires the whole component to be immersed in the solution,

including the non-coated parts. In order to quantify the benefits associated with the use of film-coated stoppers, Aptar Pharma's experts have designed a bespoke simulation experiments.

In these experiments, the stopper is inserted onto the vial and inverted, so that only the relevant coated surface of the elastomer contacts the solution (Figure 1B). As opposed to leachable studies, which are specific to a drug and only relevant to a given situation, simulation studies focus on the volatile compounds (vial filled with air), semi-volatile, non-volatile, and ionic compounds (all vials were filled with solvent and inverted). Aptar Pharma's specialists use a range of analytical methods to identify and quantify semi-volatile (gas chromatography-mass spectrometry), volatile compounds (headspace gas chromatography-Mass spectrometry), non-volatile compounds (Liquid chromatography-UV spectroscopy-Mass spectrometry), or ionic compounds (ion chromatography).

THE ETFE FILM ACTS AS A BARRIER THAT LIMITS EXTRACTABLES & LEACHABLES

Aptar Pharma's expertise in injectables is based on years of research on rubber, which led to the development of dozens of proprietary formulations of polyisoprene, styrene butadiene, Chlorobutyl, and Bromobutyl. To address the most sensitive pharma markets, such as vaccines or biologics, Aptar Pharma released a state-of-the-art 6720GC grey Bromobutyl, and ships over 1 billion components to the pharma industry annually.

Aptar Pharma has pushed the chemical performances of its closure solutions even further by developing PremiumCoat®, a platform of products that combines the 6720GC formulation with a market proven ETFE film barrier. Aptar Pharma and Next Breath* experts have performed simulation studies to compare the chemical performance of PremiumCoat® with the equivalent uncoated Bromobutyl stopper, specifically assessing the efficiency of the ETFE film itself.

Figure 2 shows the simulated profile obtained by gas chromatography of a model solvent (water/ethanol 50/50) when exposed for 6 and 12 months to a PremiumCoat® or equivalent uncoated rubber component. On these chromatograms, each peak represents a specific chemical compound that has been leached from the rubber in these model situations, to the exception of the peak corresponding to the internal standard.

Overall, the PremiumCoat® chromatogram displays fewer peaks, with a lesser magnitude than the uncoated rubber. More specifically, in the first boxed region (between 9-11 minutes of retention time) PremiumCoat® displays a 76% (at 12 months) and 80% (at 24 months) reduction in leached compounds compared to the uncoated rubber. In the second boxed region (between 13-15 minutes of retention time), a reduction of 92% (at 12 months) and 93% (at 24 months) was observed. Finally, when looking at the majority peak in the uncoated rubber profile, we observe a 97% (12 at months) and 98% (at 24 months) reduction in quantity for this specific leached compound. The latter was identified to be a Fatty Acid Methyl Ester (FAME), a by-product of the vulcanization produced through the transesterification of fatty acids, which was not reported as a toxic agent for patients.

It is particularly important to note that when performing the simulation study on PremiumCoat®, no new peak was detected as compared to the uncoated rubber. This is a clear indication that the addition of new chemical elements in the film itself did not lead to new leachables in the profile.

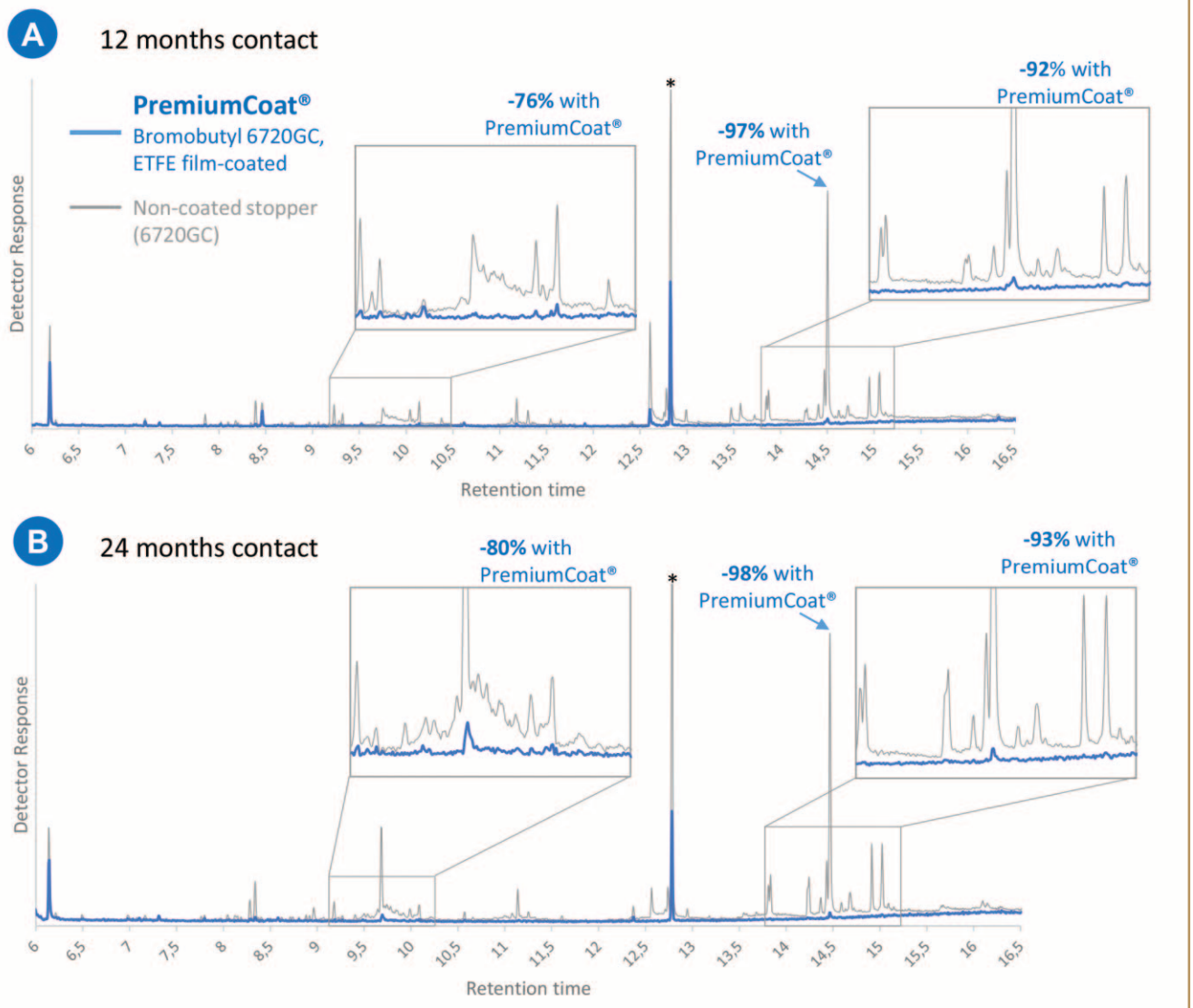
These results demonstrably show the addition of the ETFE film on the surface of the Bromobutyl rubber reduced the number and quantity of compounds leached during this simulation study by up to 97%. This demonstrates the ETFE film acts as a barrier that significantly reduces the transfer of extractables and leachables into the drug solution. Similar results led to the same conclusions when performing the same simulation experiment with gamma-sterilized components (data not shown, available in the PremiumCoat® Data Packages).

PREMIUMCOAT®: PROTECTING YOUR DRUG & YOUR PATIENTS

In this study, we reviewed the information provided by extractables, leachables, and simulation studies:

- Extractable studies are designed to provide a complete picture of all the compounds that may be transferred into the drug product. They can be performed separately from the drug development process, but because the extraction conditions are harsh, they give a poor representation of what the final use situation is.

- Conversely, leachable studies accurately represent the final use situation and confirm that the drug and closure components are compatible. They can only be performed once the final drug for-



Gas chromatogram of simulation studies comparing steam sterilized PremiumCoat® stoppers with the equivalent non-coated stoppers. Vials were filled with a 50% ethanol/water model solvent and inverted to ensure constant contact with the stoppers, over a period of 12 (panel A) and 24 months (panel B). The peak identified with a star corresponds to the internal standard but was not used for normalization as it co-eluted with a leachable found in the uncoated component. The boxed regions (9-11 minutes and 13-15 minutes) and the majority peak were integrated and the areas under the regions compared to represent the barrier effect of the film. Source: Next Breath simulation studies.[6]

mulation is defined, at the later stages of the development process.

- Simulation studies aim to inform drug developers of which compounds may actually be leached in different model situations, allowing them to anticipate much earlier in the process as to whether the closure component will be compatible with the final drug formulation.

Simulation studies are an invaluable tool for drug manufacturers who want to expedite their development process, allowing them to make informed decisions much earlier in the project, hence de-risking the choice of rubber closure component. The simulation studies performed with PremiumCoat® demonstrate the ETFE film greatly limits the number and quantity of extractables and leachables, making it a safe choice for sensitive drug developments.

Aptar Pharma has collaborated with Next Breath and other specialized service providers to produce Data Packages that provide customers with valuable information to help them choose PremiumCoat® with confidence, while accelerating the development process and regulatory approval. These Data Packages include complete simulation studies with various model solvents, glass container compatibility data, container closure integrity testing, as well as a full extractable file that

can be used for regulatory submission.

Leveraging the expertise that resides within Aptar Pharma and its service companies (Next Breath, Gateway Analytical) allows for complete and bespoke Service Packages to customers. These tailor-made packages let you choose the level of support you need in performing complete primary container testing and/or full leachable studies, so that you can focus on your formulation and smoothen your development process with PremiumCoat®.

Using simulation studies, Aptar Pharma demonstrated PremiumCoat® chemical performances. When combined with pure Bromobutyl formulation, the ETFE film-coating technology forms a barrier that reduces the quantity of leachables transferred into the solution by up to 98%. PremiumCoat® can significantly reduce the risk inherent to E&L. Choosing PremiumCoat® with Data Packages and Service Packages will accelerate your drug development process and provide the best protection for your drug and your patients.

*Next Breath is a specialty company of Aptar Pharma, and a full-service cGMP compliant laboratory specializing in analytical testing of a range of drug delivery systems from early stage to commercialization. ◆

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BIOGRAPHIES

Dr. Julie D. Suman is the President of Next Breath, an Aptar Pharma company, and Manager of Scientific Affairs for Aptar Pharma. She earned her BSc in Pharmacy and her PhD in Pharmaceutical Sciences. She is co-editor for Respiratory Drug Delivery (RDD) Proceedings, and an Affiliate Assistant Professor in the Department of Pharmaceutics, Virginia Commonwealth University, VA. A Past-Chair of the AAPS Inhalation Technology Focus Group, Dr. Suman has published in several peer-reviewed journals and presented at numerous international meetings.

Sébastien Cordier is the Technical Product Manager for PremiumCoat® projects at Aptar Pharma's Injectables division. A graduate of MINES ParisTech and EDHEC Business School in France, he first spent over 15 years in the automotive industry, where he developed a strong expertise in plastics and elastomers, before joining Aptar Pharma in 2020. In his current role as Technical Product Manager at Aptar Pharma, he is responsible for the PremiumCoat® platform of vial stoppers and syringe plungers, and is dedicated to supporting customer development projects involving coated elastomeric solutions.

Estelle Verger is the Business Development Senior Manager for PremiumCoat® coated solutions for Aptar Pharma's Injectables division and is responsible for the growth of the PremiumCoat® platform in the global injectable market. A graduate from ESSEC Business School and Fachhochschule Dortmund, with a Masters degree in International Business Management, she joined Aptar Pharma in 2011 as a Sales Manager, Injectables. She then moved to Aptar Pharma's Consumer Healthcare division as a Product Manager, where she was responsible for Airless Dispensing Solutions for pharmaceutical applications for a number of years, before returning to the Aptar Pharma Injectables division in 2020.

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2022 PDA Annual Meeting

Level Up: Agility in the New Normal

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Through plenary, concurrent, and interest group sessions, all built around the theme, *Level Up: Agility in the New Normal*, you will find out what's in store for the future of pharmaceutical manufacturing!

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- **Donna Boyce,** Senior Vice President, Head of Global Regulatory Affairs, *Pfizer*
- **Benjamin Borgo, PhD, MBA,** Head of Portfolio Management, Genome Engineering and Modulation, *MilliporeSigma*
- **Robert Dean, MBA,** Director/Team Leader, Advertising and Promotion, *Merck & Co., Inc.*
- **Kelvin H. Lee, PhD,** Director, *NIIMBL,* and Gore Professor, Chemical and Biomolecular Engineering, *University of Delaware*
- **John J. Lewin, III, PharmD, MBA, BCCP, FASHP, FCCM, FNCS,** Chief Medical Officer, *On Demand Pharmaceuticals*

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Drug Development EXECUTIVE

Nancy Lurker

President & CEO

EyePoint Pharmaceuticals, Inc.

EYEPOINT PHARMACEUTICALS

EyePoint Pharmaceuticals, Inc.: Disrupting Treatment Paradigms

With a passion for science and armed with an undergraduate degree in biology, Nancy Lurker began a career in medicine. On a path to become a doctor, she quickly realized she preferred talking to them about how to best help patients, landing her in the 1980s in Big Pharma – when the industry was on the cusp of making some profound discoveries. After more than 20 years in Big Pharma, she decided to follow her entrepreneurial spirit and transition to a smaller company. In 2016, she became President and CEO of EyePoint Pharmaceuticals, Inc., her third CEO stint, where she says she has found reward in being able to address the challenges of ophthalmic drug delivery and the benefits better eye disease treatments can provide to patients with serious eye diseases.

This past December, EyePoint announced a royalty monetization agreement with SWK Holdings Corporation for royalties payable to EyePoint under its license agreement with Alimera Sciences, Inc. for ILUVIEN®. EyePoint received a one-time $16.5 million payment from SWK in exchange for the rights to future royalties payable to EyePoint; $1.5 million will be used to advance product pipeline programs. Also in December, Ocumension Therapeutics, a China-based ophthalmic pharmaceutical company made a $15.7 million equity investment in EyePoint. Then in February 2021, the company raised another $115 million through a follow-on equity raise.

Drug Development & Delivery recently spoke with Lurker about how she is not only working to disrupt treatment paradigms in ophthalmic drug delivery, but also disrupting leadership paradigms as a female CEO of a company with 2020 total revenues of $34.4 million.

Q: What do you see as the most arduous pain point in ophthalmic drug delivery and how is EyePoint addressing that challenge?

A: People don't want to get eye injections every month or even every other month, which is the current treatment paradigm for a number of eye diseases including diabetic macular edema, wet age-related macular degeneration (wet AMD), diabetic retinopathy, and retinal vein inclusion.

All of these diseases usually are age related and are the result of dysfunction in blood flow to the eye. Our mission is to fix that. We have one drug that gets injected once every three years versus the current treatment maximum of every 3 months, and another treatment that is once per month. Other investigative treatments we're exploring would be administered once every 6 months. We believe we could go longer, but a lot of doctors want to see patients more frequently with these diseases.

Also, the eye is very small and very complex. Inserting a delivery system and making sure the drug gets to the right spot is tough. And keeping the delivery system in place is a challenge because the eye has a natural mechanism to get rid of foreign substances. Of course, there is also the challenge of ensuring that nothing going into the eye is toxic.

Q: Where have others failed in delivery development for ophthalmic drugs?

A: We believe in zero-order kinetics. This avoids the peaks and valleys of drug concentration in the eye that is common with other drug delivery platforms. One company has an implant that relies on microspheres dispersing and releasing the drug. But, that company ran into a problem when the spheres migrated to the front of the eye and patients experienced vision decline. So, the active pharmaceutical ingredient (API) worked, but the drug delivery device was breaking apart and clouding the vision. Another company using gene therapy had a patient lose their eyesight in the treated eye after 30 months. Many of the other technologies in development don't have zero-order release, meaning they release in a big burst and slowly taper down. The challenge with this method is that you get too much drug at first, and then it tapers, which may not be healthy for the eye, nor do you potentially get the best treatment outcomes. Needless to say, drug delivery to the eye is very difficult.

Q: Describe EyePoint's platform technologies.

A: Durasert® has a lot of promise. It is a miniaturized, injectable, sustained delivery system that enables local, stable, sustained delivery of a drug product in the eye over a period of weeks, months or years. We can tailor to whatever timeframe we want, depending on the drug. Some are more soluble and don't allow a sustained delivery over a period of years. We consult with physicians and patients to determine the timeframe based on their comfort levels. There are four FDA-approved products that are delivered via Durasert, and we have three more in development.

Approximately 70,000 patients have had Durasert inserted with the FD-approved products. When injected, the tiny 3mm long and 1mm wide device floats to the bottom of the vitreous and releases drug with zero-order kinetics, a consistent micro-dose delivered 24/7 over the lifespan of the implant.

Then we have the Verisome® platform technology, which offers customized, sustained, anterior delivery, from one week to several months. The platform is a biodegradable suspension liquid that forms an aqueous sphere after contact with water, such as in the eye. Verisome is suited for highly soluble compounds and shorter delivery times.

Q: What drugs are in the EyePoint pipeline that will be delivered with these platforms?

A: Already approved is YUTIQ® (fluocinolone acetonide intravitreal implant) for treating chronic non-infectious uveitis affecting the posterior segment of the eye. YUTIQ uses our Durasert technology. It is a 3mm long polymide tube into which the drug is extruded. The tube has a silicone flap on one end and is open on the other end so the API can be released at the rate we want over 3 years.

Another product in development using Durasert is EYP-1901. In December 2020, we filed the IND for EYP-1901, a potential twice-yearly sustained delivery, intravitreal anti-VEGF treatment for wet AMD. The first patient was dosed in January. EYP-1901 leverages a bioerodible formulation of the Durasert platform, which is coated with PVC and mixed with the API to get the right release rate that is controlled through diffusion. This is where zero-order kinetics is essential to achieving the optimal outcome.

Also FDA-approved is DEXYCU (dexamethasone intraocular suspension) for treating postoperative inflammation. We inject to the anterior of the eye after surgery using our Verisome technology. It will sit in place and slowly release steroid drug over 30 days. This bypasses patients having to use daily steroid eye drops and slowly taper the dosing over 30 days.

Q: Describe EyePoint's business model.

A: Our main focus is to develop drugs to bring to market, such as YUTIQ, which we developed, launched, and now manufacture ourselves. We also collaborate with Big Pharma and smaller companies that want to license our drug delivery technology. One reason people reach out to us is because it is so hard to deliver drugs to the eye. Not only does the active drug have to work, but then you layer on the delivery system, which also has to work and the risk of failure is doubled. Our partners like that four FDA-approved drugs use our Durasert delivery technology, it works, and it's safe. One of these drugs is YUTIQ, and the other three were out licensed. In these situations, we expect to get a royalty stream and milestone payments as we share in the revenues that are ultimately produced. As a matter of fact, prior to my arrival at EyePoint, everything was out licensed. The problem is you give away too much value when you do that. So, I stopped that and we now market these ourselves. We won't do 100% out licensing anymore.

Q: How are you disrupting the CEO Paradigm as a woman in STEM?

A: I am taking the lead on saying it's okay to show emotion and empathy for positive change. Women lead differently than men, and that's okay. I want to see more women and diversity on EyePoint's physician advisory boards, only when these physicians are tapped to be on advisory boards and participate in clinical trials will we get access to patients in those racial and gender groups. And, along those lines, I want to reach out to women to take the lead on clinical trial design. In pharma, and particularly in ophthalmology, the key opinion leaders are not typically very diverse. But things are getting better, and I am quite hopeful.

There is an effort in pharma to not blow this opportunity with how our reputation has improved with the pandemic. In an effort to maintain that reputation, I want to increase transparency at EyePoint. To that end, we will not significantly increase drug prices just for the sake of increasing them, we will make sure our CEO salary is not completely out of whack compared to that of the average company employee, and we will do everything we can to make sure patients get access to our drugs.

Q: Looking ahead, what is your ultimate goal for EyePoint?

A: Our goal is paradigm-changing drugs. We want to make sure what we do is changing the current paradigm on how eye diseases are treated. We do not want to be another "me too" or just add modest advancement. We want to go after serious eye diseases where patients and doctors continue to struggle to effectively treat these blinding diseases. ◆

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Special Feature

Analytical Testing Trends in 2022

By: Cindy H. Dubin, Contributor

An increasing number of clinical trial registrations, more R&D investment, growing demand for biopharma products, a continued focus on safety and quality, and more third-party testers entering the market are key reasons why the US pharmaceutical analytical testing outsourcing market is expected to reach $5.55 billion in the next five years.[1] Globally, the market could reach $12.4 billion by 2028.[2]

Specifically, bioanalytical testing is anticipated to experience the fastest growth over this period.[1] In fact, this segment led the global market in 2020 due to the high number of clinical trial registrations.[2]

This annual *Drug Development & Delivery* report reveals the innovative technologies and techniques that leading outsourcing providers currently offer for both small and large molecules.

Specialist storage for cell-based therapies at one of Catalent's bioanalytical laboratories.

Alcami: Full-Service Biologic Drug Development

Alcami offers comprehensive services to support biologic drug product development from preclinical/early-phase programs through commercial. Its bioanalytical testing services are designed to support drug substance and drug product development, validation, and routine analysis, including associated raw materials, excipients, components, and finished goods. Typical programs include therapeutic proteins, peptides, and nucleic acid products. Capabilities consist of cell-based assays with associated cell culture workflows, ELISA, electrophoresis, amino acid analysis, HPLC/UPLC with various detection modes such as UV/PDA, CAD, ELSD, RI, FLD, and MS.

"Alcami utilizes high resolution MS for intact mass analysis. We perform identity testing of post-translational modifications, glycan analysis, and peptide mapping," explains Katie Schlipp, Vice President, Laboratory Operations, Alcami. "Additionally, these products are commonly analyzed by ion pairing chromatography, ion-exchange chromatography, and PCR-based approaches."

Alcami also offers a high-throughput method development for efficient screening of solvents and columns. This platform allows Alcami to select optimal parameters quickly and develop robust and QC-friendly methods in much shorter timeframes, says Ms. Schlipp.

There are some specific key market trends that Alcami is seeing in the industry. One is the need for microbial in-use or admixture compatibility studies. A microbial in-use study is intended to evaluate the growth of a low level of microorganisms inoculated into the diluted product over the hold time to represent inadvertent contamination during rehydration or dilution of the product.

These studies determine if the product will support the growth and/or proliferation of this inadvertent contamination during the holding period prior to patient administration. "Our team of experts can support the experimental design and execution of in-use studies and provide a final scientific report for our client's filing," she says.

A second trend is an increase in the need for environmental monitoring. "The global health crisis triggered by the COVID-19 pandemic has increased the demand for sterilized pharmaceutical formulations and scientific advancements in cleanroom technology," says Ms. Schlipp. "Alcami experts can guide customers through the stringent regulatory framework associated with cleanroom space and provide support specifically tailored to the needs of each cleanroom to ensure that quality, safety, and efficacy are maintained."

She adds that a successful environmental monitoring program begins with the appropriate risk assessment, qualification, and certification activities for the space and utilities that lay the groundwork for routine testing. To this end, Alcami provides support in personnel plating, sampling performed during client manufacturing activities, and expertise in remediation efforts in case of unfortunate events such as failure to HVAC systems.

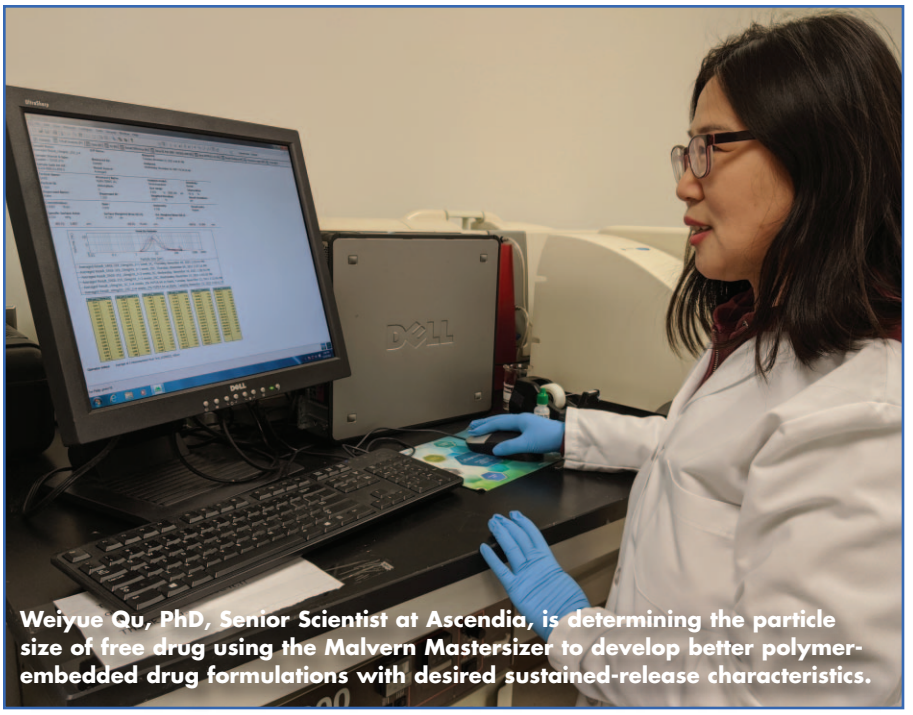
She says: "Environmental services are holistically enhanced by Alcami's microbiological services, from microbial and fungal identification to disinfection efficacy and biological indicators testing."

Beyond these capabilities, Alcami is investing in new capabilities, including analytical ultracentrifugation, variable pathlength UV for A260/A280 determinations, and new Tandem Quadrupole and QTOF instruments as part of a 16,000-square foot renovation in its Durham, NC, laboratory to be commissioned early this year.

Along with the significant investments in analytical capabilities and expansions, Alcami recently announced the acquisition of Masy BioServices. "GMP storage is a critical need in the pharma industry," says Ms. Schlipp. "Masy offers secure and tightly controlled GMP temperature storage from -196°C to 70°C, including all ICH stability conditions, for various materials including vaccines, biopharmaceuticals, cell banks, tissues, compounds, and medical devices. In addition, pharma support services through Masy include equipment calibration, large-scale validation and qualification projects, SenseAnywhere monitoring system, and equipment sales, and rentals."

Ascendia Pharmaceuticals: Rescuing Drug Development Programs

Analytical testing is a crucial part of the drug development process for both small and large molecules. And, Muhammad Asif, PhD, executive director, Analytical R&D and Quality



Weiyue Qu, PhD, Senior Scientist at Ascendia, is determining the particle size of free drug using the Malvern Mastersizer to develop better polymer-embedded drug formulations with desired sustained-release characteristics.

Control, Ascendia Pharmaceuticals, says that Ascendia's analytical testing has rescued important drug development programs. For example, Ascendia has developed methods that have predicted and helped control the *in vivo* time-dependent release of an injectable drug that precipitates at the injection site and releases slowly. "Such site-specific injections are increasingly becoming common and are made in a specific organ, joint or intervertebral space," Dr. Asif says. "These drugs are intentionally designed to precipitate or coagulate to provide maximum effect at the inject site without creating unwanted toxicity by lowering systemic absorption."

Whether testing liposomal drugs or drugs embedded in a polymer, Ascendia has methods to analyze drug content and release. High-speed chromatography such as Ultra Performance Liquid Chromatography (UPLC) and Ultra High Performance Liquid Chromatography (UHPLC) not only cut time, but also the use of organic solvents, explains Dr. Asif. Additionally, higher selectivity offered by such techniques, in many cases, allows substitution of a solvent such as acetonitrile, which has a higher toxicity with a less toxic solvent such as methanol. "Actually, Ascendia has a program in place to substitute acetonitrile with a more environmentally friendly solvent, methanol, wherever feasible."

Bethyl Laboratories: Custom Antibodies With mIHC Analysis

With 50 years of expertise in on-site manufacturing of antibodies and validation/immuno-analysis services, Bethyl Laboratories (a Fortis Life Sciences brand) has been supporting biopharma/biotech industries and academic researchers for their immunoassays-related. In-house quality control (QC) labs validate the antibodies Bethyl makes for several immuno analytical methods, such as western blot, immunoprecipitation, flow cytometry, and immunohistochemistry (IHC). Bethyl's full-service IHC lab can fix and process tissue for embedding, histological sectioning, and perform immunostaining analysis of a range of analytes. Recently, Bethyl introduced tyramide amplification system-based fluorescent multiplex IHC (mIHC) to its IHC validation/analytical services.

"mIHC is becoming a key tool in understanding cellular interactions in drug discovery and drug development process e.g., immune cells' interaction with cancer cells in tumor microenvironment," says Senior Director of Immunohistochemistry and Digital Pathology, Dr Mike Spencer, who oversees the IHC analysis services at Bethyl Laboratories. "As a result, we have invested a lot of effort into expanding our mIHC service, improving efficiency of target panel-building and optimization, and decreasing turnaround times."

He describes one of the recent services Bethyl provided to a client that needed to stain tissue microarrays containing control and pathological samples to analyze the status of immune infiltrating cells. This was done using a multiplex panel comprised of previously validated antibodies that were translated to the client's sample type. "We were able to quickly/effectively optimize an antibody panel to determine the T-cell numbers and phenotype several T-cell sub-types within the samples," he explains. "Our ability to efficiently move from optimization to immunostaining samples with our mIHC expertise saved months of time, precious samples, and other resources for the customer."

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As a Senior Director of Immunohistochemistry and Digital Pathology, Dr. Mike Spencer oversees the IHC analysis services at Bethyl Laboratories (a Fortis Life Sciences brand).

The Bethyl IHC service lab uses automated whole slide scanners for imaging of the stained tissue sections. This allows for analysis of the entire section as opposed to select regions of interest, providing for a more complete picture of markers and their spatial relationships, Dr. Spencer says. This is particularly important, as tissue heterogeneity (e.g., in tumors) is one of the leading concerns in immunostaining analysis. "The automation also allows for consistency and reliability amongst and between samples. With the combination of imaging systems in our lab, we have the capability to image single-stained brightfield images, single-plex fluorescent images, or multiplex images." These whole slide images are then uploaded to an image database, which the customer uses to view or download their mIHC data for downstream analysis.

Catalent: Innovative Mass Spec Approach Enables Faster Filing

Catalent offers a broad array of small and large molecule analytical solutions, from compendial testing to extractables and leachables and cell-based assays. Specialized capabilities include handling of controlled substances, highly-potent compounds, as well as temperature-, light-, pH-, and oxygen-sensitive APIs.

According to Jeff Schwartzenhauer, Analytical Group Leader - Product Development, Catalent, the company has extensive experience and the capabilities to perform analytical testing on a variety of dosage modalities including mRNA, mAbs, cell and gene therapy products, and several dosage forms, including solid oral dosages (capsules, tablets, softgels), inhalation products, and injectables. Catalent also has expertise in characterization, spanning techniques from residue level analysis up to higher order structure (HOS) using state-of-the-art instrumentation across spectroscopy, biophysical, bioassay, and mass spectrometry.

Additionally, Catalent offers in-house identification of visible particulates using modern Fourier transform infrared (FTIR) spectroscopy and Raman microscopes. "Our team of career forensic scientists provides a level of expertise that can rapidly assist in investigations and avoid third-party outsourced testing, which significantly reduces delays," says Todd Stone, PhD, Director, Analytical Development, Catalent Biologics.

With regard to biologics, Catalent deploys two advanced mass spectrometry (MS) analyses in support of drug substance process development and HOS. "Coverage of host cell protein (HCP) is typically performed using 2D gel assays, but suffers from shortcomings preventing a true measure of the HCP species involved," says Dr. Stone. "Catalent uses an MS approach, which provides a more thorough assessment, with depth of information on coverage, identity of HCP species, and potential quantitation that outpaces the traditional gel-based method, while shortening the timeline for analysis. For HOS, Catalent uses a covalent label to decorate molecules, followed by high-resolution MS to examine structural modifications because of stresses typically encountered in drug substance or drug product processes."

As an example, a client with a fast-track biotherapeutic required evidence that a standard HCP kit was sufficient to detect and quantify clearance in its drug substance manufacturing process, describes Dr. Stone. Proceeding with the standard gel-

based approach through a third-party lab exceeded their timeline for filing. "However, using the innovative MS-based HCP coverage approach developed and described above, Catalent was able to provide the supporting information to enable the client filing in much less time, and meet the filing deadline," he says.

Providing information relies on technology. Arvind Ramakrishnan, Director, Lab Automation, Catalent, says technology and analytics offer the ability to access raw data in near-real-time. "Having early access to data could potentially de-risk projects that could go out of specifications, which in turn, saves cost and time," he says. "Replacing outdated equipment in the lab with smart devices helps partners share data streams with sponsors in near-real-time. The resultant data streams could then be harnessed using platform technologies to not only inform sponsors on status but also positively intervene and salvage runs that are going out of specification. Catalent is actively working on proof-of-concept (PoC) ideas to increase the digital maturity of external projects."

He adds that automation and analytics approaches using low-code technologies could help generate *in silico* predictive models, even before running of the actual samples. "Having models to predict outcomes before actual sample runs could help companies avoid failure costs," Mr. Ramakrishnan says. "Catalent is working with technology partners to help meet this objective through PoC simulation work on "Lab of the Future" platforms."

DDL, Inc.: Analytical Testing of Injection Devices

When it comes to testing, devices like prefilled syringes, autoinjectors, and pen injectors have specific FDA requirements. For instance, the bulk of the requirements surrounding the physical and mechanical performance of a prefilled syringe to measure attributes such as leakage, break loose, extrusion force, and burst resistance is covered by the ISO 11040 series of standards. Many of these same mechanical and performance measurements for auto and pen injectors are outlined in the ISO 11608 series of standards.

Another key aspect of ISO 11040 for glass Luer syringes is the subject of connectivity. The manufacturing process produces a slippery and slightly irregular Luer taper, which can have issues forming a secure connection with some components. The ISO standard addresses this issue by recommending that certain Luer tests from ISO 80369-7 are conducted to demonstrate adequate connectivity to the same components, which will be attached to the syringe in the actual use situation. ISO 80369-7 replaces ISO 594.

The rapidly growing injectable market has also brought the need for more accurate Container Closure Integrity (CCI) testing to meet USP-NF<1207> deterministic CCI requirements, says Chris Murphy, Marketing Manager, DDL, Inc. The four primary deterministic tests include:

- **Helium Mass Spectrometry** – best suited for evaluating the inherent integrity of a package system.
- **High Voltage Leak Detection** – a standard approach for assessing container closure integrity of a non-porous package system.
- **Vacuum Decay Testing** – applicable to any package containing headspace, including, but not limited to, parenteral vial packages, screw-capped bottles, autoinjectors, and flexible bags or pouches.
- **Headspace Analysis** – Assessment of package headspace via laser-based analysis techniques provides a quantitative, nondestructive measure of oxygen, carbon dioxide, water vapor, or internal pressure in a nonporous, rigid or non-rigid package's headspace.

Additional testing, which accounts for drug/device interactions, will likely need to be performed to bring a prefilled syringe product to market includes:

- extractables and leachables;
- USP particulate matter identification and determination;
- ISO 11607 package validation; and
- stability studies to determine product shelf-life.

Metrics Contract Services: Sensitive Detection for Challenging Compounds

More and more APIs are entering the clinical phase with no chromophore or possessing a very weak chromophore, says Jerry "Jr." Mizell, Senior Director of Analytical Services

at Metrics Contract Services. "The need for methods that have adequate sensitivity for assay and impurities could pose a substantial issue," he explains. "Having other means of detection on an HPLC system, such as charged aerosol detection (CAD), refractive index (RI), and mass spectroscopy (MS) will be critical going forward to be successful with challenging compounds."

As an example, he says Metrics was recently challenged by a clinical project with a very simple API structure containing no chromophore and highly reactive when exposed to water and several other organic solvents. In addition, one of the known impurities and a process intermediate were mutagenic and had to be controlled and analyzed at very low levels (ppm). Several approaches had to be taken for assay and impurity analysis including gas chromatography, RI, and MS. Diluent selection and sample preparation were challenging due to the reactive nature of the active. "But, all challenges were overcome with successful method development and validation for all methods."

Mr. Mizell adds that MS is also a valuable tool for a CDMO to possess as the FDA's requirements for nitrosamines is a requirement that all NDA filings must meet. "The same can be said for elemental impurities as it behooves a CDMO to possess ICP-OES and ICP-MS instrumentation," he says.

Salubrent: GCHS & GC/MS Capabilities Handle Complex Projects

"Salubrent Pharma Solutions is a recently formed CDMO focused on supporting the shift toward biologics and personalized medicines, where small batch fill and finish services, combined with continuous batch-fed API processes and just-in-time/direct-to-patient delivery, will ensure patients are never without the life-saving therapies they require," says Anand Padmanabhan, Director of Analytical Development at Salubrent. "To this end, Salubrent has built its analytical services lab to meet the needs of this changing paradigm."

In addition to its broader offering of small-molecule analytical testing methods, Salubrent has assembled a team of scientists, and specific instrumentation, focused on large-molecule analytical method development. One specific challenge developing these therapies is the identification of impurities in drug substances and finished goods. Mr. Padmanabhan views gas chromatography (GC) as a vital analytical technique in this effort because of its ability to separate the organic volatile compounds of a sample mixture (typically drug substances) and detect them, thus determining their presence or absence and/or how much is present. "GC is also helpful in the determination of potency, dissolution rate, cleaning verification, etc. in instances where compounds cannot be detected using HPLC UV," he adds.

Analysis for actives that do not have a UV chromophore cannot be detected using HPLC alone. "In this area, GC is a useful tool, and by adding mass spectrometry (MS), this instrument becomes even more powerful in the identification of impurities," according to Mr. Padmanabhan. "Overall, a compound is identified via GC-MS not only by comparing its retention time to a standard (GC), but also by using its mass spectrum, making GC in combination with MS an extremely powerful analytical tool."

GC/MS analysis has endless applications in material testing, identification, and certification. Identification of organic volatile impurities is one of the main applications. In the pharmaceutical industry, GC/MS is used in research and development, production, and quality control. In medicinal chemistry, GC/MS is used in the synthesis and characterization of compounds and in pharmaceutical biotechnology.

"Salubrent has the GCHS and GC/MS instruments analysis capabilities and expertise necessary to handle these types of complex projects," says Mr. Padmanabhan, adding that he views Salubrent's ELISA testing, Malvern Mastersizer particle size analysis, and HPLC with PDA impurity and assay potency quantitation capabilities as key to supporting the industry's increasing focus on biologics and personalized therapies.

SGS: Sophisticated Instrumentation for ID Testing

SGS has three centers of excellence in North America that offer analytical testing for biologics – located in Pennsylvania, Illinois, and Ontario, Canada – providing services at every stage of a product's lifecycle, from

Analytical scientist at SGS Health Science, in Lincolnshire, IL.

early-phase cell bank safety assessment and product characterization to later phase method development and final phase GMP product release.

For the last seven years, SGS's chemistry laboratory in Lincolnshire, IL, has extensively used Pinnacle PCX, a post-column derivatization system from Pickering Laboratories that performs analysis of amino acids for individual raw materials as well as the evaluation of small peptides. This instrument replaced the thin layer chromatography (TLC) test used in the past to monitor ninhydrin positive substances, explains Natalia Belikova, PhD, Analytical Services Director, SGS. "High Performance Liquid Chromatography instrument (HPLC) technology is more specific than TLC, has better sensitivity, is faster, and costs less. This instrumentation was also successfully used for identification tests for small peptides, when identification is based on molar ratios of known amino acids and presence/absence of other known amino acids."

Additionally, the SGS laboratory has an X-ray powder diffractogram D2-phaser (XRPD) from Bruker that is used extensively for the identification of different known polymorphic forms of small molecules. "It also allows us to evaluate API purity," she says. "Several clients have asked us to run confirmatory testing that polymorphic structure of active pharmaceuticals ingredients does not change when an API is incorporated into the final drug product during the manufacturing process. This methodology is useful when clients ask us to evaluate if stability storage (under International Conference on Harmonization or accelerated studies) affects the polymorphic form of active ingredient."

Triclinic Labs, Inc.: Chemical Analysis & Solid-State Development

Triclinic Labs provides both cGMP and non-cGMP materials characterization of organic and inorganic molecules. The lab has a DEA-Controlled Substance Registration for Schedule I-V compounds and offers a variety of techniques, including PXRD, NMR, TGA, DSC, DVS, SEM, EDX, IR, FT-IR, Raman (Dispersive, Low Frequency), optical, digital, hot-stage, and polarized microscopy, optical rotation, contact angle, particle size and quantity analysis, HPLC, GC with headspace, ICP-MS, and a variety of other techniques for identifying chemical composition, contaminants, and unknown substances.

Determination of crystalline in amorphous mixtures is a requirement of the FDA to demonstrate control in chemical manufacturing (CMC). Aeri Park, PhD, Chief Scientific Officer, Triclinic Labs, explains that Triclinic has developed innumerable quantitative methods to determine the presence or absence of crystalline polymorphs in solid mixtures at extremely low levels of detection, and well below the FDA's typical 5% w/w request. These methods are then used to release materials for pharmaceutical drug product manufacturing. ◆

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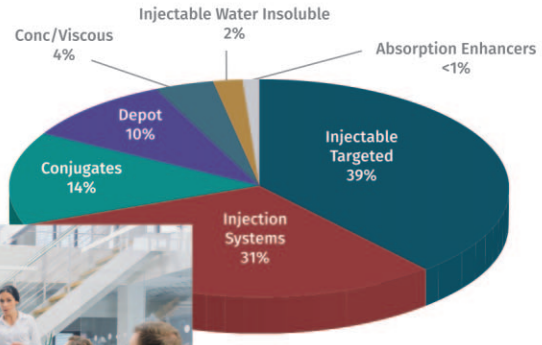

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CYBERSECURITY

Cybersecurity for Connected Medical Devices: A Holistic Approach During the Entire Product Lifecycle

By: Nicola Alagia

INTRODUCTION

Cybersecurity is a topic that periodically gets headlines when a new category of devices connects to the Internet or creates a local network to provide added value to the end user. For example, due to the increase of personal computers connected to the Internet and the introduction of services that deal with sensitive data, there has been a gradual shift from HTTP (not secure) to HTTPS. For about 10 years, we have become accustomed to being connected to the Internet 24/7 with our smartphones; these devices are therefore a target of hackers who daily attempt to find security flaws. This is also true for automotive, Industry 4.0, IoT, and medical devices: a new era of connected devices.

The following focuses on cybersecurity issues relating to medical devices that are rapidly becoming more connected. Larger medical devices are connected to the hospital network, and they exchange patients' personal data and the results of analyses and therapies with other devices inside the same network. Smaller medical devices directly used by patients can send logs and other personal data to smartphones (or directly to a server in a cloud), in order to monitor the therapy, and to share the information with family members and doctors. We are in the midst of the Digital Health transition, but not all medical devices were designed with security at the beginning of their development lifecycle.

The following explains why cybersecurity is important for connected medical devices and how to integrate ad hoc activities to tackle cybersecurity in the early phases of product development. The risk management drives the design choices, guiding the development teams in balancing a systematic approach with a systemic and holistic viewpoint of the entire system.

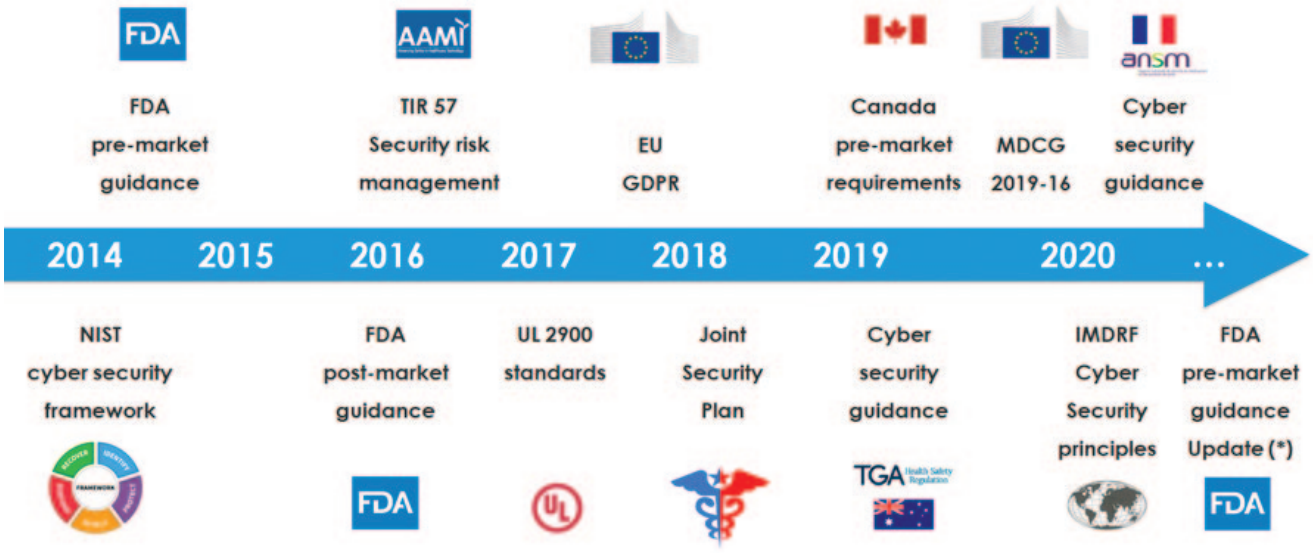
WHY ATTACK A MEDICAL DEVICE?

An attacker might have several reasons and opportunities to target a medical device. The data stored or transferred by the device often has value (eg, personal data). The hacker might be interested in modifying data or in altering functionalities of the medical device. The effect of such attack could be a safety harm for the patient, or economic damage to the healthcare facility that is prevented from using the medical device.

An opportunity to target a medical device originates from the growing complexity of the modern devices and, in particular, of the firmware and software they embed. Operating systems and communication protocol libraries are commonly integrated into medical devices as third-party software but, due to the vulnerabilities of such off-the-shelf software, the medical device inherits the same software vulnerabilities. A famous example is the ransomware WannaCry, which spread across thousands of personal computers including hospital facilities and their medical devices.[1] The attackers took advantage of a weakness in the Microsoft Windows operating system, and were able to finalize the attack because those devices remained unpatched for a long time. During the pandemic, the number of ransomware attacks has increased, and cyber-criminals have shifted their target from random individuals to large companies. Recent attacks disrupt operational technology (OT) of those companies, and here are just few examples from recent news: Healthcare and Public Health Sector, Colonial Pipeline, JBS, Bose.[2-5]

Finally, considering that cybersecurity is a relatively new topic for connected medical devices, it follows that insecure devices could be selected by hackers as easy targets. Hackers could use medical devices as a starting point for more complex attacks, sim-

FIGURE 1



Key regulatory documents released after the NIST cybersecurity framework.

ilar to what happened with Mirai malware.[6] It infected home routers and IP cameras, using them to launch a DDoS attack on various servers across the Internet.

SAFETY, SECURITY & C-I-A

The C-I-A triad stands for Confidentiality, Integrity, and Availability, and is the basis of information security. Confidentiality indicates the protection of data and information at rest or exchanged between a sender and one or more recipients; Integrity is the guarantee that the data has not been altered at rest or during transmission from the sender to the recipient; Availability indicates precisely the availability of data and services for users who are authorized to use them.

Since 2014, regulators' attention to cybersecurity has been increasing. Manufacturers are required to take care of security risks and mitigations during the development of the medical device, and are required to monitor for new vulnerabilities when their devices are on the market. Figure 1 shows a subset of resources available to medical device manufacturers from national and international regulatory or working groups.

In order to assess and control the risks that may impact the basic safety and essential performance of medical devices, manufacturers apply the ISO standard 14971:2019 (Application of risk management to medical devices).[7] Figure 2 shows the link between cybersecurity and safety: confidentiality can be associated with the concept of privacy, while a lack of integrity and/or availability can compromise the safety of the medical device.

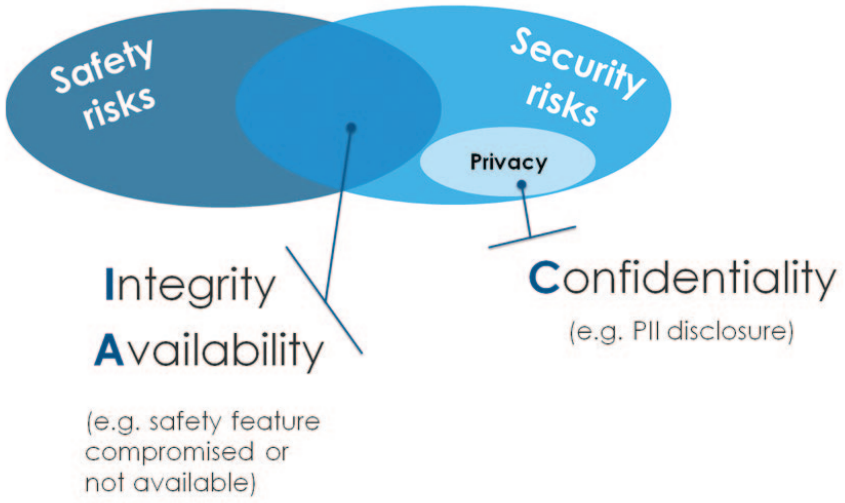
For this reason, the AAMI TIR57:2016/(R)2019 (Principles for medical device security - Risk management) suggests executing the security risk analysis in parallel to the safety risk analysis.[8] Each output of one analysis (eg, a new risk control measure added to the system) shall be checked and verified against the other risk analysis. For example, adding an encryption algorithm that is too demanding for the medical device might impact its performance and so might impact its safety.

FRAMEWORKS FOR MANAGING CYBERSECURITY

A widely used framework for managing cybersecurity risks is the one proposed by NIST in 2014.[9] The NIST framework is not specific to the medical industry but helps organizations to integrate cybersecurity into their processes. The framework defines the activities to be implemented to manage cybersecurity (core functions and categories) and defines criteria to assess the maturity level (tiers) of organizations. The five basic functions defined as "core"- Identify, Protect, Detect, Respond, Recover - have inspired many of the subsequent standards or guidelines indicated in Figure 2.

Premarket submission guidance issued in 2014 by the Food and Drug Administration, in the US, suggests guidelines for managing cybersecurity in medical devices during the design phase.[10] Manufacturers can take their cues from some of the mitigations proposed for the Identify and Protect functions, such as user authentication, role and privilege identification, ses-

FIGURE 2



Relationship between safety and security.

sion timeouts, and software/firmware updates with digital signature mechanisms. For the Detect, Respond, and Recover functions, the guidance suggests that the devices be able to detect attacks, track them in logs, and, most importantly, still be able to provide the basic safety and essential performance capabilities for which they were designed. An updated draft of the guidance was released in 2018; it focuses on the security testing that manufacturer should perform and document to ensure that security measures are implemented, are effective, and do not introduce safety risks.[11] The emphasis on testing is also evident when reading the table of contents of UL 2900-1 and UL 2900-2-1 (which the FDA has recognized as applicable standards:)[12-15]

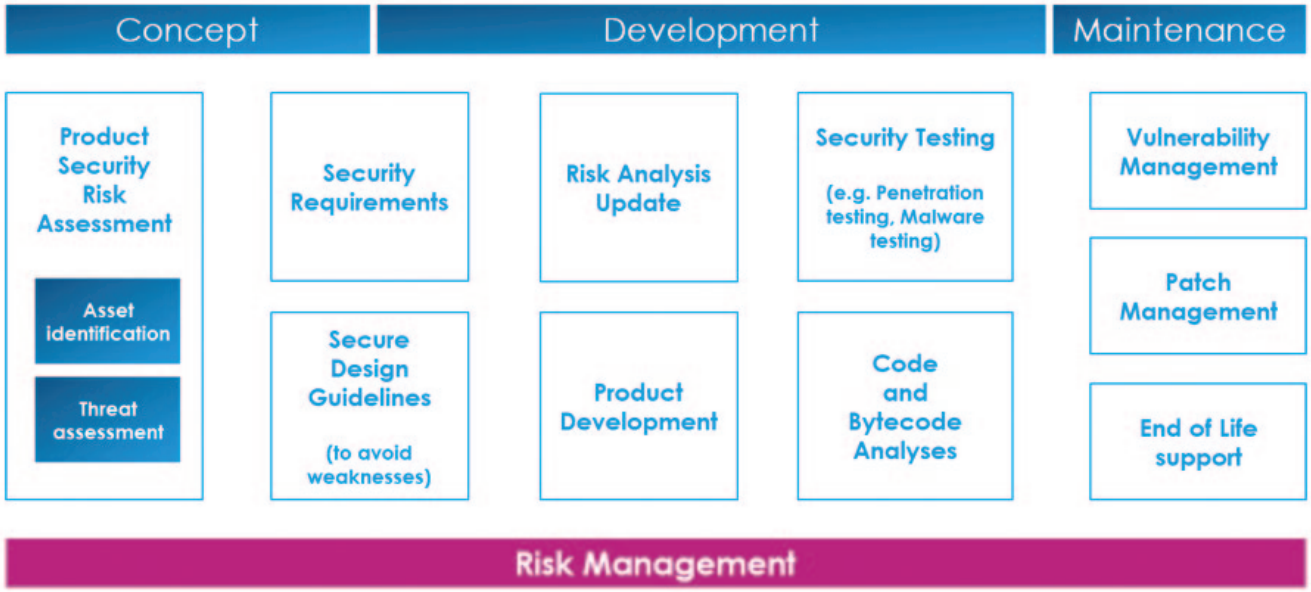
- Known vulnerability testing
- Malware testing
- Malformed input testing
- Structured penetration testing
- Software weakness analysis
- Static source code analysis
- Static binary and bytecode analysis

Other updates in the draft premarket guidance are about the level of documentation that manufacturer should provide as evidence that they have designed and implemented security features correctly. Furthermore, it is required that each single design decision is derived from a rigorous risk analysis activity as described in the following section.

It is worth mentioning that most of the guidelines have the following common points to tackle the cybersecurity issues of a medical device:

- the risk analysis is a key activity to conducted throughout the entire development process
- a secure design development shall be established
- security testing shall be executed

FIGURE 3



Simplified product development process and key security activities.

- all the activities shall be documented properly
- the end user shall be notified about security features and risks of the medical device
- manufacturers shall monitor their devices on the market for new vulnerabilities that might be found and might cause risks for the patients

SECURITY RISK MANAGEMENT

Figure 3 shows a simplified framework inspired to the one proposed by the Joint Security Plan in January 2019.[16] The JSP highlights the need to manage risk management activities during all phases of development and, very importantly, even during device commercialization. If the device's safety analysis can be considered valid throughout the life of the device, with regard to cybersecurity, it is necessary to re-evaluate the analysis periodically because new vulnerabilities are constantly being discovered. A device classified as secure the day it is approved for commercialization may no longer be so in the following months.

AAMI TIR57 (Principles for medical device security - Risk management) defines guidelines for:

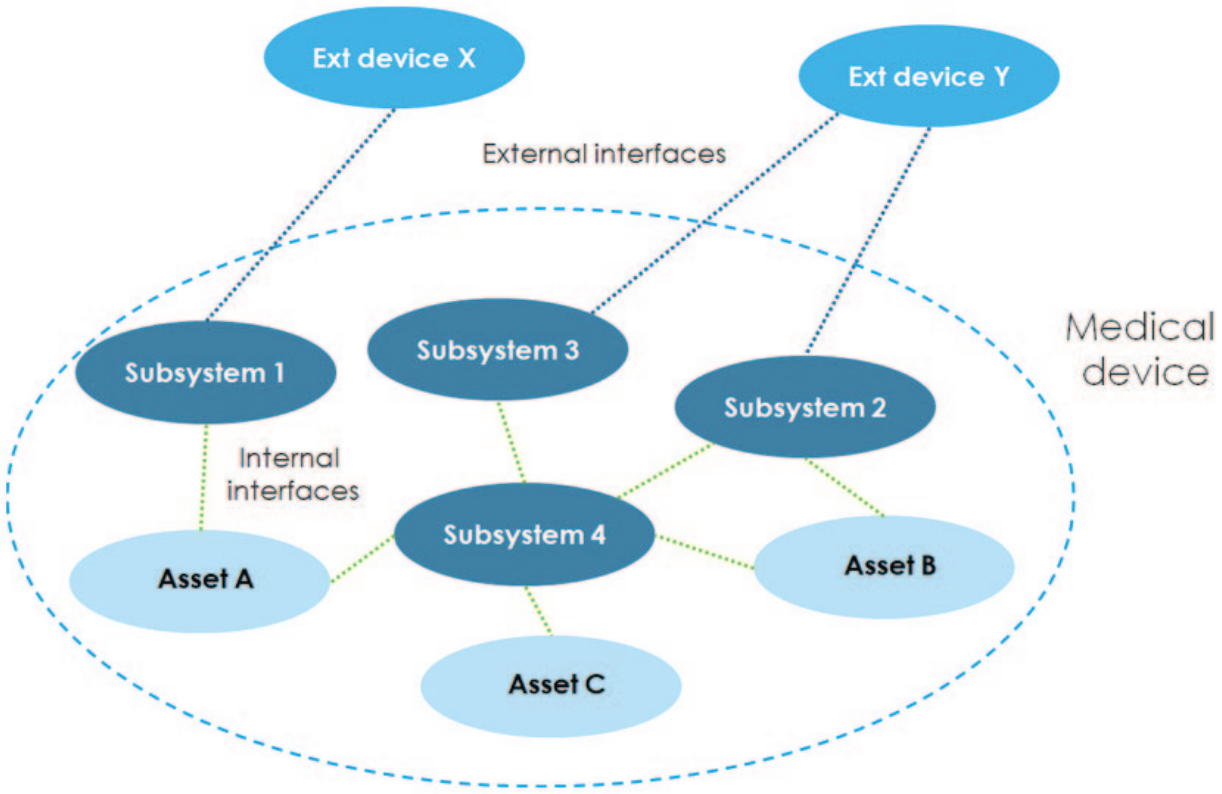
- identifying assets, vulnerabilities, and threats
- assessing risks
- evaluating countermeasures,
- monitoring effectiveness

Note that TIR57 proposes a new definition of harm, expanding the one introduced by ISO 14971 (physical injury or damage) by adding the concepts of reduction of effectiveness, breach of data, and system security.

In the initial phases of a project, it is useful to identify the assets to be protected, and to evaluate the communication channels of the device with the external networks. When the system is fully described, the next step is the threat modeling, ie, the evaluation the possible threats and vulnerabilities that could affect the assets. Examples of assets (also suggested by TIR57) are the software itself that guarantees the functionality of the medical device, the encryption keys, the digital certificates, the user data, the logs, the configuration data, the communication interfaces, etc.

When a complete description of the system is available, it is useful to also analyze the internal interfaces. The example shown in Figure 4 highlights that the "Subsystem 3" of that hypothetical medical device does not have a direct link to any asset, but its relationship with "Subsystem

FIGURE 4



External and internal interfaces of a system and their links to the assets.

4" might allow an attacker to access the three assets of the device. For this reason, the internal interfaces between "Subsystem 4", "Subsystem 3", and "Subsystem 2" shall be carefully analyzed and, if they are really necessary, they shall be secured properly.

An output of the Security Risk Assessment activity is the definition of the Security Requirements that implement the risk control measures identified during the risk assessment. These requirements impact the system architecture and, subsequently, the product development, its verification, and validation.

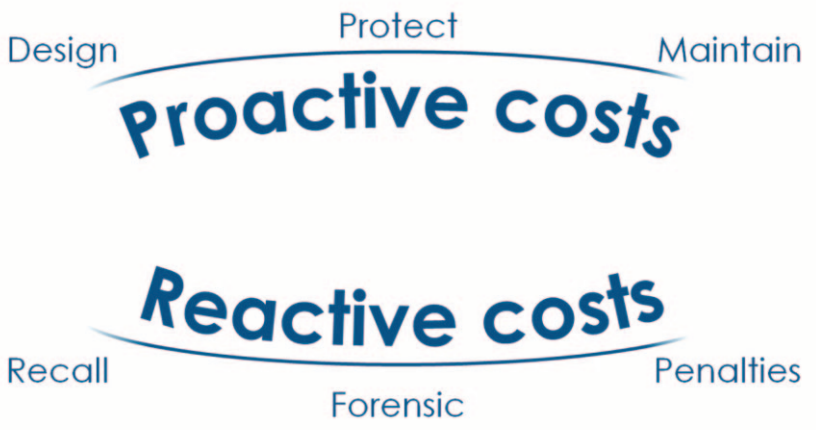
Cybersecurity is not synonymous with cryptography, which represents only one of the possible Cybersecurity tools. It is not an exclusively software matter. In fact, many disciplines contribute to design a device that is inherently secure. Physical protection can be added to the device, limiting access to communication ports. Specific electronic components, such as secure elements, can be integrated in the design in order to protect keys and sensitive data, and to implement cryptographic functionalities. Usability is also important because the security mechanisms should be transparent for the end user, or at least should not compromise the overall user experience.

MANAGING THE COST OF CYBERSECURITY

The security-related activities added to a design lifecycle do not come for free. They require additional costs to design and protect the medical device during the development phase. They also require a structured maintenance plan to monitor new vulnerabilities and apply security patches as necessary. These can be classified as proactive costs. But if something goes wrong, manufacturers might face reactive costs for a recall campaign, complicated forensic analysis or, even worse, penalties.

The right approach is to invest in proactive costs, designing a secure device from the beginning. In addition, reactive costs are generally higher than the proactive costs. Reactive costs may also have a negative effect on the brand reputation.

FIGURE 5



Managing the cost of cybersecurity.

SUMMARY

Cybersecurity should be managed during the entire life cycle of a project, from the initial idea, through the marketing of the product, and post-sales support. This is the suggested approach to design and maintain a safe and secure device.

The design team shall include product security experts to conduct security risk analysis properly, to help define an architecture that includes security control measures, to perform design review, to execute security testing, and to plan maintenance activities. The system engineer leading the project shall contribute by approaching the cybersecurity with a holistic mindset. Safety and security risk management activities shall be conducted in parallel, identifying the security risk control measures that should be translated into System Requirements or Software Requirements.

Several guidelines specific for the medical industry are available upon which device manufacturers can rely to define their own secure product development lifecycle.

Note: This article is based on an article published in Viewpoints Newsletter of AISE, the Italian chapter of INCOSE, Issue 6, 2018. ◆

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BIOGRAPHY

Nicola Alagia is a Senior Systems Engineer who has been working for Flex in the medical industry for more than 13 years, focusing on software development and cybersecurity. He currently leads a multidisciplinary team in Flex's Milan Design Center to integrate cybersecurity and regulatory requirements into product development. He graduated with a degree in Telecommunications Engineering from Polytechnic University of Milan. He also attended a 1-year post-graduate master in Information and Communication Technology studying solutions to secure the forthcoming mobile ad hoc networks (similar to the modern Zigbee and BLE mesh networks). Prior to Flex, he worked as firmware engineer for Pirelli Broadband Solutions, an Italian telecommunications company.

Drug Development
EXECUTIVE

Jeff Moses
Chief Marketing Officer
GATC Health

Ian Jenkins
Director of Science
GATC Health

GATC Health

GATC Health & Liquid Biosciences: Faster, Cheaper, More Effective Drug Discovery

Drug prices are often driven by the high level of risk and an uncertainty in drug development, along with the lengthy timeline – a process that may ultimately require millions of man hours and billions of dollars.

Therefore, to save costs and time, GATC Health and the company Liquid Biosciences are collaborating to leverage genomics, predictive algorithms, and biomarker discoveries. They aim to help pharma companies accelerate biomarker discovery and identify potential treatments while minimizing risks and reducing costs. Each company brings its unique offering to the partnership: GATC Health focuses on whole genome/expresome testing, drug discovery, and new molecule development using a proprietary technology platform while Liquid Biosciences is at the forefront of using predictive algorithms in biomarker discovery.

GATC Health is a pioneering technology company using Predictive Multiomics™ to advance drug discovery and improve human health. The company's proprietary Multiomics Advanced Technology™ (MAT) platform analyzes billions of biological data points, including whole genome/exome data and multiple omics to make accurate predictions about disease states and individual response to diseases and treatments.

Drug Development & Delivery recently spoke with Jenkins and Jeff Moses, GATC Chief Marketing Officer, about the combined benefits of their MAT platform and Liquid Biosciences' Emerge mathematical evolution platform. These two platforms help identify the right biology sooner and focus on a smaller set of potential compounds early in the pre-clinical development process to enable pharma

companies to develop drugs with more efficiency and a higher success rate.

Q: What do you see as a pain point in pharma and how are GATC and Liquid Biosciences working to address that?

Ian: There are two big pain points in pharma right now. One is the standard model that 95% of pharma relies on, which is finding a semi-functional molecule and giving it to patients in massive quantities in hopes that it will reduce a symptom or group of symptoms. That works for about 90% of drugs and has served us well in the past, but can be time consuming and expensive. Pharma is becoming frustrated using this model because it's expensive and not particularly effective. Especially with more complex disease processes, like chronic disease states, this model has become less and less effective. The second big problem in pharma is the difficulty of minimizing side effects. Recently, a major pharma company had a drug that they spent 8 years and $3 billion developing and it had a negative side effect when they took it to clinical trials. They wound up shutting the entire drug operation down. So, you're looking at huge risks, large quantities of money, and a flawed, antiquated system. This is causing all the pain: time consuming, expensive, and unintended side effects. The idea behind what we are doing is to eliminate those "pain points" that inhibit the speed to market and the efficacy of drugs.

Q: What is meant by Predictive Multiomics and how do you apply that to the human body?

Ian: This is essentially a digital imprint of a human. GATC utilizes Predictive Multiomics, which means we are looking at many different biomes, or biological components, of the whole human body to create a virtual human. From a physiological standpoint, we take a more holistic view of a human to predictively model what may happen with a new drug in the human model before it's given to a human. To break it down more simply, by imprinting the disease state over the top of our human model, we can have a large interactive predictive model that determines what the biotarget and the biotarget pathway looks like, what's around it, and how it interacts in the body. Secondarily, our technology can see whether or not the drug will be binding to, or affecting, unintended locations or sites. We can also look at this quantitatively to determine how much drug is effective and as important, how much is needed.

Q: How does digital human testing compare to traditional lab testing?

Ian: GATC's predictive model saves a lot of time because the work goes much faster when you are running a digital model. For example, a typical drug model may take 7 million man-hours. We are taking about 1.5 million of those hours and condensing them down to three weeks. So, our unique technology shortens the time frame and reduces costs for speed to market. We can get from raw biodata (sampling), or biopsy, of the diseased tissue to potential drugs in about three weeks.

Some pharma companies would take thousands of molecules and manually test them at the target in the lab. That is a very time-consuming process. However, in our platforms, we are looking at the function of the biotarget. The GATC platform can view hundreds of thousands of targets and focus on only the ones most likely to interact and make interaction predictions using neural networks and decoding models to have real-time interaction modeling. It's a significant difference in time. We're talking about potentially taking years and years down to a few days as the platform matures.

Q: Can you explain how GATC, Liquid Biosciences, and a pharma partner work together? Once a molecule is discovered, what happens next?

Ian: It all starts with a sample or group of samples taken from disease patients. This is typically initiated by the pharma partner. This sample is processed into raw data. Liquid Biosciences runs a program that is akin to an "evolutionary environment." Basically, there are competing species that are algorithmic so that the best algorithm surfaces. That algorithm defines the vector analysis of a biotarget. So, raw data comes in and the target is defined at Liquid Biosciences. Once the target is discovered, all of the data is sent to the GATC's Multiomics Advanced Technology platform where it is analyzed in the context of the whole human. We take the target and the raw data and create potential drug targets and a model for interaction. That may look like a small molecule or a larger protein hormone, in the case of immune components. GATC's platform looks at proteins, molecules, and other interventions that can affect a biotarget. The model we create goes back to the pharma partner where they take on digital validations and cellular validations and plug them back into the human model. When a pharma partner uses GATC, they go straight from not knowing much about a target to having a really good place to

start and a set of specific tools to use. Sending the information back and forth allows us to aid them in the clinical trial component to help differentiate patient responses and minimize side effects.

Jeff: On the first project we worked with Liquid Biosciences, in less than a couple of months, we were able to assess biomarkers (potential targets) and identify new molecules that could eventually become the basis for a treatment or drug for that particular disease state. We are in the process of patenting these new molecules. In this example, we believed that we saved our partner at least 20% in development time. Under the old model, Liquid Biosciences would identify the biomarkers and the pharma partner would go back into the lab to trial-and-error their way through proteins, compounds, or molecules to try to find something that was effective.

Q: What therapeutic treatments can be positively impacted by this, and can you share an example?

Ian: The biggest impact will be in hormonal imbalances, immune challenges, and in identifying key triggers to these for earlier prevention. While the core of that is being able to save time and money, this also allows us to address what we haven't been able to do before from a pharmaceutical standpoint. For example, we identified an addiction molecule for a drug company that gave biopsied tissue data to Liquid Biosciences. They then were able to identify a probable group of targets and an equation that represented a trigger point. We took that information and incorporated it to create a quantitative shift in the biomarkers and the underlying factors involved with addiction in general. We took one addictive model, which was a stimulant-based addiction, and tracked the underlying mechanistic actions of addiction. We found a unique way to address addiction from a mechanistic approach. From there, we were able to grab a component of known molecules and recombine them in a way to achieve a high predictive affinity and create a shift in biotargets to remodel the limbic system and erase the damage of addiction. A lot of times in addiction you are looking at stopping a craving. What we need to do is treat it by remodeling the damaged part of the brain; restructuring the brain with a more specified mechanism. This is a very different way of approaching addiction and we believe these molecules will be able to do it. It's a combination of molecular signaling and immune-driven mechanisms that ultimately create the shift.

Jeff: Addiction is difficult to treat and has a lot of moving parts. It's not a simple disease model. Our platform's ability to think in a biological context gives us a leg up in being able to address these things in a unique, non-linear manner.

Q: What role can the GATC and Liquid Biosciences technologies play in personalized medicine?

Ian: The goal of our company is to turn this into a personalized approach. I think, in time, this will become the way we do medicine – analyzing these key biomarkers on the individual to find the perfect molecule for that specific individual. In our Perfect Molecule Program we've started looking at predictive modeling for the individual based off the genome and expressome to determine a one-to-one relationship. Right now, it's a one to many, but we're narrowing it down to groups of people. We are currently working towards using our technology to treat the individual, essentially making the perfect drug for the individual. Our ultimate goal is to have a complete one-to-one relationship between disease prediction and intervention or treatment per patient. This is a major step in that direction.

Q: In addition to identifying new molecules, what are other capabilities for your technology?

Jeff: Liquid Biosciences and GATC are stand-alone companies that also operate independently of our joint venture. Combined, what we are doing is really unique and revolutionary. Aside from GATC's work in drug discovery and development, we have developed and are currently selling consumer-focused DNA test kits that provide personalized reports for specific disease states for health issues. Current, GATC produces a Viral Immunity Platform™ (VIP) that can tell an individual's risk, response and after effects of viral infections, like COVID-19. We also offer a detailed Health & Wellness platform and a Depression/Anxiety platform and just announced our Diabetes platform. In the near future, we will also introduce a Cardiac Risk platform.

Ian: There are two uses for our technology: detect a disease earlier, or before it starts, and treat it or prevent it better. We are detecting faster, earlier, and treating better. We have a non-obvious way of approaching a disease. We can look at a disease with less bias, which allows us to find a less common route to treating a disease. ◆

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GALECTIN INHIBITORS

Is a Galectin-3 Inhibitor the Answer for Millions of Patients With Cirrhosis & Cancer?

By: Pol F. Boudes, MD

INTRODUCTION

First described in 1971, the galectin-3 protein has since been implicated in the progression of a wide range of different human diseases, such as cancer and cirrhosis. For instance, galectin-3 plays a significant role in liver diseases, such as non-alcoholic steatohepatitis (NASH) and its complication, liver cirrhosis.[1] Could development of a galectin-3 inhibitor become a treatment for the millions of people affected by these diseases? Galectin Therapeutics has spent the past decade researching this very question. The company recently enrolled its first patient in a Phase 2B/3 clinical trial to test whether its novel galectin-3 inhibitor, belapectin, has the ability to prevent the development of esophageal varices in patients suffering with NASH cirrhosis.[2]

GALECTINS

Galectins are a class of proteins that act as a molecular glue in the body, bringing together molecules that have specific sugars on them. There are 15 galectin protein subtypes, all with the common characteristic of binding to galactose-containing carbohydrates and glycoproteins. The most relevant galectin for human diseases is galectin-3.[3]

While galectin-3 is normally expressed in small amounts in many different cell types, it is highly expressed in macrophages of the immune system and activated by tissue damage. Chronic inflammation in organs such as the liver, for example, can trigger galectin-3 to promote the development of scar tissue, which over time can interfere with organ function.[3]

Galectin Therapeutics set out to discover whether using a galectin-3 inhibitor, belapectin, could break this cycle of disease.

GALECTIN-3 & DISEASE

Medical science is recognizing the role that galectin-3 plays in a wide range of diseases. There were few scientific articles written about galectin-3 in the 1990s and 2000s, but nearly 150 in 2010 and more than 300 in 2018. These articles encompass the role of galectin-3 not only in liver fibrosis, cirrhosis, and cancer, but also diabetes, heart attacks, lung fibrosis, and many other diseases.[1]

Published data substantiating the importance of galectin-3 in the fibrotic process arises from gene knockout experiments in animal studies.[4] Mice genetically altered to knock out the galectin-3 gene, and thus unable to produce galectin-3, do not develop liver fibrosis in response to toxic insult to the liver.

GALECTIN-3 & LIVER FIBROSIS & CIRRHOSIS

In the liver, fibrosis – or the excessive deposition of collagen – is the end result of multiple inflammatory conditions and infections. Progressive liver fibrosis leads to cirrhosis, which is characterized by a disruption of the normal architecture of the liver, resulting in reduction of liver function, multiple medical complications, and ultimately death. More than 500,000 patients have

cirrhosis in the US, with close to 50,000 losing their lives each year.[5]

Scientific evidence strongly suggests that galectin-3 is essential for the development of liver fibrosis and, ultimately, NASH and NASH cirrhosis.

In non-alcoholic fatty liver disease (NAFLD) – the precursor to NASH – fat starts to build up in the liver. The fat buildup causes inflammation, an immune response of the body to protect against attack. In this stage, galectin-3 becomes highly expressed. The presence of galectin-3 triggers liver scarring, causing liver fibrosis. As the fibrosis displaces healthy liver cells, the cells begin to die. The continued scarring and liver cell death causes cirrhosis. At this stage, liver function is reduced, even to the point of failure.

Currently, there is no treatment for NASH cirrhosis short of a liver transplant, and only a fraction of the patients with cirrhosis are able to get a liver transplant, a highly expensive procedure.[6] As a result, there is an urgent need for treating NASH cirrhosis.

THE ROLE OF GALECTIN-3 IN CANCER

Galectin proteins, notably galectin-3, are also present in increased amounts in cancers of many types. In fact, expression of galectin-3 appears to be higher in the majority of solid tumors including skin (melanoma), head and neck cancer, and lung cancer (such as non-small cell lung cancer).[3]

Examining tumors for the presence of galectin-3 has gained some acceptance in clinical medicine. In thyroid cancers, pathologists routinely stain tumor biopsies for galectin-3 to distinguish malignant tissue from normal tissue, potentially reducing unnecessary thyroid surgeries. It has also been shown that the amount of galectin-3 expressed in some cancers, such as lung cancers, correlates with the aggressiveness of the cancer and the ultimate prognosis of the patient, subject to confirmation, a finding that may be useful in clinical practice and help with the choice of treatment.[7]

Galectin-3 promotes the spread of cancer in the following three ways:

- Invasiveness - Galectin proteins help cancer cells migrate and therefore favor the infiltration of the cancer cells into surrounding tissue.

- Metastasis - In colon cancer, the highest levels of galectin-3 are found in tumors that have metastasized elsewhere in the body, while the lowest are in the cancer cells located in the original tumor.

- Tumor Growth - Galectin-3 reduces cell death and promotes the growth of blood vessels that bring blood supply to the tumor.

Galectin-3 also inhibits the patient's immune system, thereby preventing immune cells from killing tumor cells.8 This immune effect of galectin-3 in cancer is particularly interesting because of the rising importance of cancer immunotherapy. Could a galectin-3 inhibitor play a role in fighting cancer? This hypothesis is currently being tested in the clinic by combining belapectin with an immune checkpoint inhibitor in patients with melanoma and head and neck cancer.[9]

FINDING THE RIGHT GALECTIN-3 INHIBITOR

It is one thing to recognize an opportunity for a galectin-3 inhibitor, but it is another to take advantage of it. More than a decade ago, Galectin Therapeutics began researching molecules with the potential to act as inhibitors to the disease-causing properties of galectins, particularly galectin-3.

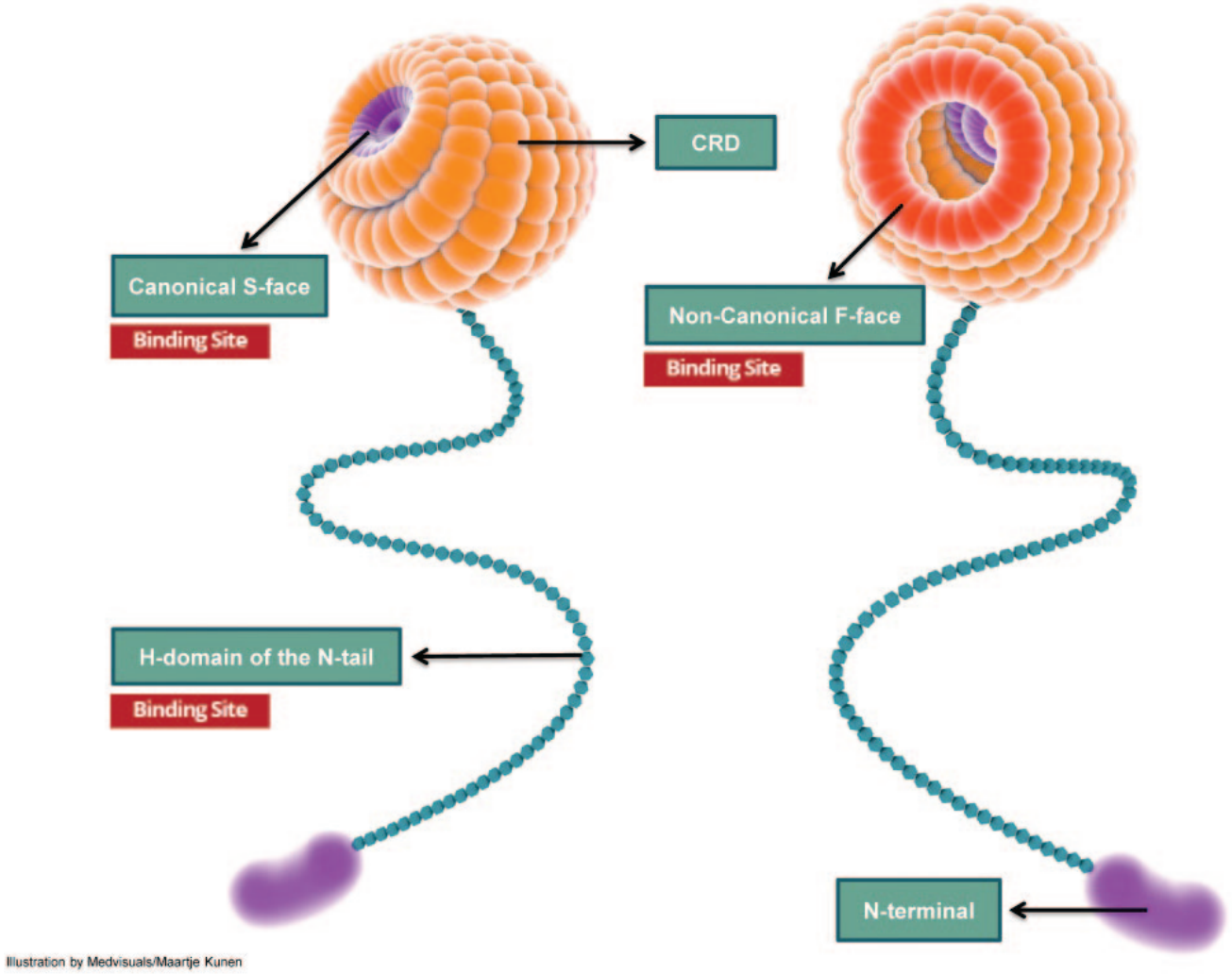
UNDERSTANDING THE GALECTIN-3 BINDING SITE

The first step was to understand the galectin-3 binding site, which is found in cells throughout the body. The binding sites internal to the cells were not useful to Galectin Therapeutics' purposes, but the binding sites found on the external surface of cells and in free-floating galectin-3 molecules were both potentially actionable.

Galectin Therapeutics began with a survey of the existing chemical literature on the galectin-3 binding site, soon expanding to undertake basic research at the University of Minnesota to understand the chemical structure of the galectin-3 receptor.

The galectin-3 natural carbohydrate binding site (CBD) exhibits poor druggability, making it an unsuitable target for the more typical small molecules used in pharmaceutical treatments. It is a big, diverse binding site when compared to more discrete receptors, where a small drug molecule might fit like a lock and key. The propensity of galectin-3 to bind to sugars, notably at other sites on the molecule (Figure 1), suggests that a larger molecule derived from a carbohydrate might be better suited as a potential drug candidate.[10]

FIGURE 1



The galectin-3 molecule has a globular head attached to a slender long N-tail, presenting several potential binding sites. The canonical S-face binds to lactose and similar molecules, while larger molecules, such as Galectin Therapeutics' belapectin galectin-3 inhibitor, bind to the non-canonical F-face and the H-domain of the N-tail.[10]
(Figure based on Suthahar N, et al. Theranostics 2018; 8(3): 593-609. doi: 10.7150/thno.22196)

IN SILICO MODELING

Much of the initial search for suitable molecules was done using state-of-the-art in silico methods, where computer models were used to screen drug candidates for their physical and chemical properties to interact with galectin-3 and the carbohydrate recognition domain. Galectin Therapeutics began with existing molecules but soon went on to design de novo new molecule structures that weren't yet known.

Because of the poor druggability of the galectin-3 CBD site, Galectin Therapeutics believed that carbohydrate chemistry held the answer to creating a different type of galectin-3 inhibitor. Galectin-3 is a large molecule itself and offers other options for binding sites in addition to the single CBD. The flexibility of a complex poly-carbohydrate structure meant such a molecule might have greater interaction with multiple binding sites on the galectin-3 molecule.

Galectin Therapeutics set out to create such flexible molecules that would bind to galectin-3 and thereby prevent the development of scar tissue and the other deleterious effects. Computer models were used to predict the chemical interactions of candidate molecules with the galectin receptor itself.

The predictions of the in silico modeling were confirmed with *in vitro* testing, the results of which were used to refine the computer models.

This was not a trivial effort. Nearly 1,000 molecules were examined, not only for their galectin-3 binding abilities but also for affinity to other galectins. Extensive studies were required to characterize the physical, chemical, and biological proper-

ties of potential drug candidates utilizing state-of-the-art analytical techniques and methodologies, some of which were developed in collaboration with leading scientists in the academic field of carbohydrate research. Galectin Therapeutics has patented many of these new molecules. The first molecules, such as belapectin, will be delivered as infusions, and oral follow-up compounds are currently early in the development process.

ANIMAL STUDIES

Ultimately, Galectin Therapeutics had to show that the molecule actually worked *in vivo* to change the disease process. That called for animal and, eventually, human testing.

To do that, Galectin Therapeutics had to first synthesize a large amount of belapectin, a kilogram or so. Working in vitro might require only micrograms of the molecule, but animal and human testing requires much more. The process also requires good analytical test methods to ensure the purity and quality of the substance, and it must be delivered in a form that can be given to an animal.

The endpoints of the study must also be chosen carefully. Because galectin-3 works at the tissue level, there wouldn't be a demonstrable change in the levels of circulating galectin-3. The drug levels could be tracked, but there was no way of knowing whether the drug was having an effect by looking at the amount of galectin-3 in circulation. Instead, Galectin Therapeutics had to undertake in-depth preclinical experiments, trying to induce a disease in a cohort of mice and seeing whether a candidate molecule had any effect on the disease progression. This takes time – around 8 months from start to finish – to dose the animals, give time for the disease progression, then follow up with tissue analysis (histology) and data analysis.

Two drug candidates underwent extensive animal testing for use in liver disease, and one molecule, belapectin, showed such strong results in preclinical testing that in 2013, the FDA allowed it to enter into human clinical trials for NASH and gave it the coveted Fast Track status.

HUMAN CLINICAL TRIALS IN NASH CIRRHOSIS

After many years of research, Galectin Therapeutics recently launched its NAVIGATE study, an international, seamless, adaptively designed Phase 2b/3 clinical trial of its galectin-3 inhibitor belapectin, the company's lead compound, in NASH cirrhosis patients who have clinical signs of portal hypertension and are at risk of developing esophageal varices.[11] A previous Phase 2 study, the NASH-CX clinical trial, had shown belapectin could prevent the development of new varices in this patient population. To the best of Galectin Therapeutics' knowledge, belapectin is the first compound to demonstrate clinically meaningful positive effects in patients with NASH cirrhosis without esophageal varices.

Unlike most other ongoing clinical trials focused primarily on earlier stages of NASH, the NAVIGATE study population will comprise patients with compensated liver cirrhosis. NAVIGATE is focused on patients who have not yet developed esophageal varices but are at increased risk of developing these potentially life-threatening complications. Consequently, patient selection for both Phase 2b and Phase 3 will be based on clinical signs of portal hypertension such as a depressed platelet count (thrombocytopenia), an enlargement of the spleen (splenomegaly), and evidence of collateral vessels.

The primary endpoint of the trial is to assess the effect of belapectin on the incidence of new varices. A centralized review system of video recording of esophagogastroduodenoscopy (EGD) has been put in place, and the primary endpoint will be adjudicated by expert EGD readers. Key secondary endpoints will assess the type of varices (sizes and/or bleeding) and other clinical events, such as ascites, hepatic encephalopathy, listing for liver transplantation, or death.

HUMAN CLINICAL TRIALS IN OTHER INDICATIONS

The potential of belapectin as a galectin-3 inhibitor attracted the attention of researchers working in cancer immunology. Galectin-3 is intimately involved in the progression of cancer, perhaps interfering with the immune systems' ability to find and destroy cancer cells. Providence Cancer Institute has been testing belapectin in a Phase 1B investigator-initiated trial in combination with KEYTRUDA®, a checkpoint inhibitor (anti-PD-1) immunotherapy, to treat advanced melanoma as well as head and neck cancer. Preliminary data from this open-label study shows a 50% objective response rate in advanced melanoma with belapectin in combination with KEYTRUDA. There is also a suggestion that the combination could reduce the incidence of auto-immune reactions, a well known and sometimes problematic side effect.[12] These results are encouraging, and additional data are ex-

pected soon.

The response rates observed for this combination therapy in advanced melanoma and head and neck cancer patients appear better than with KEYTRUDA alone, particularly given the low response rates of anti-PD-1 monotherapy in head and neck cancer.[13] There is a significant clinical need for better options for these patients.

KEY LEARNINGS

Galectin Therapeutics has validated the applicability of using a galectin-3 inhibitor in treating fibrosis in liver cirrhosis, a validation that drug developers call the "proof-of-concept."

Galectin Therapeutics scientists also made the compound available to colleagues working in selected areas, generating data showing the molecule worked in various models of renal fibrosis, pulmonary fibrosis, and even cardiac and select forms of vascular fibrosis.

The ongoing work at the Providence Cancer Institute likewise shows the impact a galectin-3 inhibitor might have in modifying the body's immune response to cancer when used in combination with a check-point inhibitor.

For its part, Galectin Therapeutics continues its basic research on new molecules, targeting both galectin-3 and other galectins. These would be follow-on compounds for belapectin, notably to develop an oral formulation of a galectin-3 inhibitor. To this end, the company established Galectin Sciences LLC as a joint partnership with SBH Sciences in Natick, MA, a contract research organization that had been involved in much of the earlier preclinical research that had led to belapectin. Galectin Sciences continues research to find non-carbohydrate small molecules that can inhibit galectin molecules, with the goal of developing oral therapies. ◆

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BIOGRAPHY

Pol F. Boudes, MD, is Chief Medical Officer of Galectin Therapeutics. Dr. Boudes has more than 25 years of experience in clinical drug development in immunology, endocrine, metabolic, orphan, and liver-related diseases, and he has contributed to the approval of multiple drugs, both in the US and globally, across a variety of therapeutic indications. Before joining Galectin Therapeutics, Dr. Boudes was the Chief Medical Officer at CymaBay Therapeutics, where he worked on the company's proprietary NASH compound and was instrumental in inventing and launching programs in rare liver diseases. Dr. Boudes earned his MD at the University of Marseilles, France. He completed his internship and residency in Marseilles and Paris, was an assistant professor of medicine at the University of Paris, and also participated in multiple clinical research programs as an investigator. He is certified by the Educational Commission for Foreign Medical Graduates (US) and board-specialized in endocrinology and metabolic diseases, internal medicine, as well as in geriatric diseases (Paris).

BIOMARKERS

Biomarkers: The Guiding Light for R&D in Heterogeneous Diseases

By: Thomas Turi, PhD

BIOMARKER-LED R&D

While biomarkers have been a long-standing part of R&D and a mainstay of clinical practice for the characterization and diagnosis of disease for decades, they are increasingly playing a crucial role in guiding decisions to improve efficacy and efficiency of clinical trials. Biomarkers can not only provide critical insights into the biological activity of targets and their modulation, but can also guide on the most appropriate patient populations to recruit into studies and inform the selection of trial metrics and endpoints.

The pharmaceutical industry has emerged from a period of poor productivity and overall inefficiency to deliver an unprecedented number of new drugs. In 2006, after extensive research and consultation, the US Food and Drug Administration issued the Critical Path Report and List.[1] The report outlined a number of priority areas for scientific improvement in the development process, including the development and utilization of biomarkers,

FIGURE 1

Ongoing investment in state-of-the-art technology, Nexelis executes high-throughput testing with automation. We support our scientists in the laboratory with automated workflows and robotics to aid in our precision and accuracy.

as well as modernizing clinical trial methodologies and processes.[1] Incorporating many of the recommendations from the Critical Path Report, throughout the past 5 years, the industry has delivered an average of 46 new approvals per year, more than double the 22 approvals per year delivered between 2006 and 2010.[2]

Through this marked improvement, biomarkers have demonstrated their integral role in enabling better decisions on advancing compounds with a high probability of success and eliminating nonproductive programs at earlier stages of development. Thus, a biomarker-led R&D approach has become the standard for drug development.

Biomarkers have already guided our understanding of the complex heterogeneity of several cancers and led to the development of a number of precision medicines. More recent drug approvals, in highly heterogeneous solid tumors such as colorectal cancer, are now targeting smaller patient populations – representing even single-digit percentages of patients with aggressive cancers and poor prognoses.[3] Unsurprisingly, most major pharmaceutical companies are increasing their investment in biomarker-guided development.

Practically, this means ensuring a comprehensive biomarker approach is initiated during the preclinical phase of the program and integrated into the overall clinical development strategy. Implementation of the biomarker strategy should begin within the very first patient cohort, evaluating whether there are early signals of efficacy, or potentially early signals of safety issues. This will ultimately allow earlier, more informed decisions on whether to proceed into late-stage human trials, thus saving time, money, and resources.

PLUGGING INTO THE RIGHT EXPERTISE AT THE RIGHT TIME

The pharmaceutical industry has made great strides in unlocking the potential of biomarkers in oncology, but how can researchers quickly make the same inroads in other heterogeneous diseases that have multiple biomarkers at play? One route is to access a partner, such as a clinical research organization (CRO), with deep, relevant therapeutic and biomarker expertise, and then harness this knowledge at an early stage when designing biomarker-led clinical programs.

CROs are in a unique position, with experience supporting clinical development programs that span a broad spectrum of disease and mechanistic approaches. Moreover, many of these CROs have expertise in developing robust, complex biomarker assays. Identifying the right laboratory partner with the knowl-

FIGURE 2

26,000-sq-ft CAP/CLIA-certified facility dedicated to bioanalytical and biomarker assays.

edge and capabilities to design and run these critical assays needed to support the clinical trial design could be the difference between trial success and failure.

It is also important to access this expertise early on. In order to capture as many insights as possible, many trials incorporate numerous types of markers, and therefore multiple invasive tests for the patient to endure, which can result in an unnecessary burden on the patient. Having the insights, knowledge, and experience to select the most informative and valuable biomarker and utilizing enhanced technologies to interrogate each sample through multiplex assays, can all help to streamline biomarker analysis and decrease patient burden.

CROs can be seen as thought partners, able to lend the right expertise and resources to alleviate the burden for in-house development teams. Accessing a range of biomarker scientists and technical experts, many of whom are core members of any CRO team, complements a sponsor's translational medicine expertise, bolsters early research efforts, and supports a more informed decision-making process. In this way, the right CRO partner provides added value and efficiency to development programs.

APPLYING A BIOMARKER-LED APPROACH TO NASH

Biomarkers can provide a dynamic and powerful approach to understanding the spectrum of a heterogenous disease, such as in nonalcoholic fatty liver disease (NAFLD). NAFLD causes fat to accumulate in the liver of people who drink little or no alcohol. It is increasingly common around the world, especially in Western nations, and it is set to become the predominant cause of chronic liver disease in many parts of the world. The epidemiology and demographic characteristics of NAFLD vary worldwide.[4,5] In the US, it is the most common form of chronic liver disease, affecting about one-quarter of the population.[4]

Nonalcoholic steatohepatitis (NASH) is a type of NAFLD and a condition that causes inflammation and accumulation of fat and fibrous tissue in the liver; it develops in only in a minority of patients with NAFLD. NASH is thought to be the precursor of liver fibrosis, which is associated with morbidity and mortality.[6] Nearly 16.5 million people in the US are believed to have NASH, with more than 3 million thought to have liver cirrhosis due to NASH.[7] Globally, one-quarter of the population is estimated to have NAFLD.[8] The incidence of NASH is projected to increase by up to 56% in the next 10 years.[9]

One major challenge in successfully developing an effective treatment is the lack of a noninvasive approach to diagnosing NASH/NAFLD. Currently, the only means of a diagnosis is through invasive liver biopsies, but the interpretation is often subjective and the patient acceptability is poor.[10] Variability in sampling that results from the limited sample size in combination with the heterogeneity of the disease also limits the chance of a successful and

FIGURE 3

Experts in esoteric biomarker assay development and large-scale testing through Phase 4 clinical studies.

FIGURE 4

Industry-leading specialty laboratory with a focus on infectious disease, immunotherapy, and metabolic diseases.

definitive diagnosis.[10] As the prevalence of NASH continues to grow, it is becoming increasingly important to identify noninvasive biomarkers that support both diagnosis and the measurement of disease progression.

Furthermore, reflective of the complex nature of this disease, there are currently no approved treatments. This means that, when a patient goes through the burdensome process of diagnosis, they are then faced with few, or even no, medical effective interventions to help treat this disease. Currently, doctors can only recommend weight loss to treat NASH – according to the National Institute of Diabetes and Digestive and Kidney Diseases, weight loss can reduce fat in the liver, inflammation, and fibrosis.[11] Experts are not sure why some people with NAFLD progress to having NASH. The continued lack of understanding of the underlying molecular mechanisms that contribute to NAFLD, and subsequently NASH, make it increasingly difficult to develop a viable therapy.

The significant unmet medical need in NASH has led to substantial interest from the pharmaceutical industry, patient organizations, and physicians on the development of an effective therapy. Yet the intricacy of the disease creates a complexity in the development of clinical studies that can be difficult to address.

A large number of noninvasive biomarkers have been deployed to evaluate NASH status and liver function, and those specifically targeting liver fibrosis provide a novel tool that can both determine a patient's likely journey with the disease and ascertain treatment efficacy.[12] These types of biomarkers could also be used to risk-stratify patients and improve the prognostics of clinical trials, to target the most at-need and at-risk patients, in turn, increasing the likelihood of trial success.

Additionally, numerous studies have attempted to identify informative biomarkers for NASH disease staging, progression, and potential disease regression. Recently, a transcriptomic approach identified a set of promising biomarkers that correlate to disease stage. Additional proteomic analysis demonstrated that AKR1B10 and GDF15 are associated with both hepatocyte ballooning and inflammation scores.[12] These serum-based protein biomarkers can be useful for the confirmation and staging of NASH in future clinical studies. Access to validated assays for these novel and informative biomarkers could also provide valuable insights on the efficacy of emerging therapeutics.

In addition to monitoring drug action or response, biomarkers are increasingly being utilized to guide patient selection, treatment, and management decisions. Prognostic biomarkers can help identify patient populations that are more likely to respond to a given treatment, while safety biomarkers can help avoid administering treatment to patients who might not respond, or may be harmed, by a specific

treatment. As selection biomarkers are used more frequently in clinical development (presently, they are only being used in a small proportion of studies), and patient selection is subsequently refined, phase transition success rates in high-prevalence diseases should improve.[13] The higher success rates for trials involving biomarker-selected patients suggest the broader industry is already on the right path.[13]

In one recent independent study, high levels of fibrogenesis biomarkers, such as PRO-C3, in patients with NASH are indicative of high disease activity and can be used to improve patient response rates in clinical trials. In a study presented at EASL 2018, patients' specific levels of PRO-C3 were significantly reduced as a result of resmetirom (a selective thyroid hormone receptor-β agonist) treatment. Similar predictive results for resmetirom were presented by Madrigal Pharmaceuticals at the Global NASH Congress 2020 in the extension study.[14] As a result, specific PRO-C3 levels have been listed as inclusion criteria for the Phase 3 NAFLD clinical trials.[14] This new paradigm further demonstrates the utilization of biomarkers in the assessment and treatment of diseases at the earliest possible time could maximize the benefit to patients.[15]

Bringing a safe and effective NASH treatment to patients poses many challenges, but through strategic partnerships between pharmaceutical and CROs, leveraging critical expertise and substantial resources, it is achievable.

As our understanding of heterogeneous diseases evolves, the use and value of biomarkers in research and development will only continue to increase as we seek to unlock our understanding of these diseases and develop increasingly personalized treatments. ◆

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BIOGRAPHY

Dr. Thomas Turi joined the executive leadership at Nexelis in the role as Chief Scientific Officer, bringing 25 years of pharmaceutical and contract research leadership experience. Two of his previous accomplishments are when he established the Biomarker Center of Excellence for Covance, and when he served as Senior Director of Translation Biomarkers and Mechanistic Biology at Pfizer. In addition to his current responsibilities, he has served on the Board of Trustees for The Life Sciences Foundation and is a member of the Global Health Research Roundtable of the Indiana Clinical and Translational Sciences Institute. He has previously served on the Board of Directors for Caprion Proteomics and led several external partnerships, including those with Rules Based Medicine, Celera, Incyte, and Affymetrix. He has also served on grant and program project review boards for NASA's Section for Biotechnology and Tissue Engineering. Dr. Turi earned his bachelor's degrees in Biochemistry and Chemistry from the University of Illinois at Urbana-Champaign and his PhD in Molecular Genetics from the University of Cincinnati College of Medicine. He completed postdoctoral training at the Yale University School of Medicine applying molecular genetic techniques to investigate the mechanisms of protein transport.

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With the global rise of chronic diseases and the COVID19 outbreak, increasingly complex drug products are being tested and launched on the market. Choosing the right primary packaging and closure solution is essential to facilitating regulatory approval and fast time-to-market. Building on 70 years' experience in the development and manufacturing of drug packaging solutions, **Aptar Pharma** offers end-to-end services, accelerating and de-risking the choice of closure component. Our PremiumCoat® Service packages address key customer challenges at different stages of their drug development. Leveraging our state-of-the-art PremiumCoat® technology, internal capabilities, expertise, and knowledge of the drug development journey, Aptar Pharma offers three packages to support the validation of PremiumCoat® with your glass container (Platform Package) or your specific drug (E&L Package). The Development Package accompanies our customers through their validation process, to ensure their success. For more information, visit Aptar Pharma at **www.aptar.com/pharmaceutical/.**

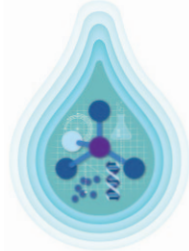
Formulation Development

Ascendia Pharmaceuticals is a speciality CDMO dedicated to developing enhanced formulations of existing drug products, and enabling formulations for pre-clinical and clinical-stage drug candidates. We specialize in developing formulation solutions for poorly water-soluble molecules and other challenging development projects. Combining our extensive knowledge and experience of formulation capabilities with our suite of nano-particle technologies, we can assess the feasibility of a broad array of robust formulation options to improve a drug's bioavailability. Thusly decreasing the amount of drug and the number of injections and greatly reducing in some cases the daily pill-burden from 20 to 4. Ascendia's expertise spans across (IV, SC, or IM), injection, ophthalmic, transdermal, nasal delivery, along with immediate- and controlled-release products for oral administration and complex generics. For more information, visit Ascendia at **www.ascendiapharma.com.**

Platform Technology

Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 11 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.com.**

Bioavailability & Development Toolkit



From its three early phase drug development centers of excellence in Nottingham, UK, Somerset, NJ, and San Diego, CA, and its network of manufacturing facilities, Catalent offers its customers end-to-end solutions, encompassing early drug product formulation and dose form design, through to clinical supply services, commercial-scale manufacturing and lifecycle management. For early development, these solutions include analytical, preformulation and formulation technologies, and Catalent offers the most comprehensive bioavailability enhancing technology toolkit including lipid formulation, spray drying, and hot melt extrusion. Its experience sees Catalent support the development and launch of over 150 new products every year. By adapting for each molecule's unique characteristics and challenges, Catalent uses its expertise and a wide range of tools and technologies to create dose forms that benefit patients. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

Differentiated Injectable Delivery

Credence MedSystems is a medical technology company focused on delivering medications safely for the benefit of our patients, caregivers and partners. The Companion Safety Syringe System was born from Credence's core philosophy of *Innovation Without Change*. By providing passive safety and reuse prevention while using existing primary package components, the Companion offers best-in-class drug delivery with a vastly simplified path to market for our biotech and pharmaceutical partners. The Companion is available in luer needle, staked needle and dual chamber reconstitution configurations. In all cases, the user performs the injection, receives end-of-dose cues and then the needle automatically retracts into the syringe, which is then disabled. For more information, contact Credence MedSystems at 1-844-CMEDSYS, email info@credencemed.com, or visit **www.CredenceMed.com.**

Hands-On Formulation Support

GATTEFOSSÉ

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

Device Development Services

Neuma is an engineering services company focused on the development of robust, verifiable, reliable, and manufacturable drug delivery devices. Neuma turns developing and innovative drug delivery technologies into commercially successful devices. Neuma has extensive experience with novel, custom, and platform device adaptations across prefillable syringes, autoinjectors, reconstitution devices, and wearable injectors. Neuma provides Design for Production (DFP) services, addressing the Design for Testing, Design for Sterilization, Design for Manufacturability, and Design for Assembly requirements that are often overlooked or neglected in the development process. Neuma's device experts are ready to transform your technology into a medical solution. To learn more about Neuma and its parent company, Kymanox, visit neumaengineering.com and **www.kymanox.com.**

Functional Chemicals

MITSUBISHI GAS CHEMICAL

Mitsubishi Gas Chemical (MGC) is a leading company in the field of functional chemicals, such as oxygen barrier and absorbing polymers. MGC established the Advanced Business Development Division in 2015 for tackling a variety of today's problems, and the division created OXYCAPT™ Multilayer Plastic Vial & Syringe to solve some issues of existing primary packaging for injectable drugs. OXYCAPT Vial & Syringe consists of three layers. The inner and outer layers are made of cyclo-olefin polymer (COP), the most reliable polymer in the pharmaceutical industry. The middle layer is made of state-of-the-art polyester developed by MGC. The oxygen-barrier property is almost equivalent to glass and much better than COP. OXYCAPT also provides an ultra violet (UV) barrier. For more information, visit Mitsubishi Gas Chemical at **www.mgc.co.jp/eng/products/abd/oxycapt.html.**

Injectable Drug Delivery

OWEN MUMFORD
Pharmaceutical Services

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

Global Data & Analytics

PharmaCircle is a leading provider of global data and analysis on the pharmaceutical, biotechnology, and drug delivery industries. PharmaCircle's premier database delivers an integrated scientific, regulatory, and commercial landscape view with unprecedented access to hundreds of company, product, and technology attributes. PharmaCircle connects product and pipeline information for drugs and biologics with formulation and component details, and provides due diligence level data on nearly 6,000 drug delivery technologies and devices. Drug label comparison tools and full-text document search capabilities help to further streamline research. No other industry database matches PharmaCircle's breadth of content and multi-parameter search, filtering, and visualization capabilities. To learn more, email contact@pharmacircle.com, call (800) 439-5130, or visit **www.pharmacircle.com.**

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Alcami Corporation	27	sales@alcaminow.com	www.alcaminow.com
Aptar Pharma	9	Info.pharma@aptar.com	www.aptar.com/pharmaceutical
Ascendia Pharma	2	bd@ascendiapharma.com	www.ascendiapharma.com
Captisol	11	cdinfo@captisol.com	www.Captisol.com
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Optimal formulations are built on the science of understanding your molecule's bioavailability challenge and art of finding the best technology match.

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